

Xenografts: are the risks so great that we should not proceed?

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ABSTRACT – Animal organs could save patients needing transplants, but further research is necessary to resolve remaining problems with organ rejection. Furthermore, xenotransplantation risks transmitting animal pathogens to patients and to the general population. It would be unethical to proceed with clinical trials before principles and procedures for dealing with this risk are in place.

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1. Introduction

There is a critical shortage of human organs available for transplantation [1–3]. Transplants of animal organs are seen by many as an ideal solution to this problem [2]. The potential benefits of a successful xenograft program therefore appear to be considerable. A successful supply of xenografts would in theory allow an unlimited supply of suitable organs and tissues. The organs could be sized to fit the transplantation. The transplantation could be performed as an elective procedure with therefore better preparation of the patient. There would also be more time to do testing on the animal donor for potential infections compared to the current situation with human transplants, where testing is necessarily limited because of the short time available between identification of the donor and the transplant organ into the recipient [1–4].

However, xenotransplantation raises major ethical concerns. It is morally imperative that these concerns be resolved before going forward with research. Some of these, such as questions about informed consent and animal welfare, are common to other kinds of medical research. Our primary focus in this article will be the distinctive scientific challenge posed by xenotransplantation, the potential for disease transmission to third parties, and its moral fallout.

Xenotransplantation may transmit microorganisms (including currently unknown or unrecognized ones) from

animal tissue or organs to transplant recipients [3–9]. Such infections could potentially be transmitted from person to person, putting the general population at risk as well. The effects of these new infections could be devastating, as the human population would be unlikely to have any immunity to these new infections.

Data from xenotransplants to date are necessarily limited because of the very small numbers of these transplants that have been performed so far and poor follow-up. There are, however, numerous examples of the transmission of microorganisms (and viruses in particular) from animals (or animal tissues) to humans by means other than xenotransplantation [3–17]. Transmission has occurred both by direct contact with animals as well as through the use of biological materials designed for medical purposes [3, 16] (e.g., SV40 that contaminated many of the early poliovirus vaccines derived from monkey kidney cells). Once established into a new human host, then human to human transmission has occurred for many of these agents [3, 10, 11, 16, 17] (e.g., HIV, influenza, hepatitis B, SV40).

There are therefore already well-established risks in addition to other theoretical infection risks with the use of animal products (such as xenografts) in people. The major scientific questions relevant to the ethics of xenotransplantation are whether these risks are just theoretical and whether there is some way of quantifying these risks.

2. Immunological hurdles

Primates, because of the relatively close similarity of their organs to human organs, would be theoretically the best donors to use in humans if rejection was to be

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minimized. However, because of ethical considerations (paradoxically their closeness to humans), concerns about the higher likelihood of transmission of simian viruses compared to other animal viruses as well as major problems with supply, it is unlikely these will be a large source of organs for transplantation in the future [1]. Pigs currently appear to be the most likely animal to be used as an animal donor, although to date hyper-acute rejection has been a major hurdle that has limited the use of not only pigs but also other animal species other than primates, as donors for humans [18, 19]. Hyper-acute rejection occurs within a few minutes of the organ being transplanted. It is the result of xeno-reactive natural antibodies that activate complement [7, 18]. These antibodies protect us against animal viruses and make up a relatively large percentage (more than 2%) of total circulating human IgM and IgG [7]. They bind to a polysaccharide surface antigen (gal α 1-3gal). This is a galactose-containing antigen present on the cells of all mammals other than primates [7, 18]. In experimental animals genetic engineering has modified many of the critical genes involved in this form of complement dependent rejection [7,18]. These genetic modifications are designed to remove or modify this polysaccharide antigen on the surface of pig cells (i.e. humanize the pig cell surface) or through the insertion of human genes, to prevent complement activation [7, 18]. However, the genetic modifications of these antigens and other cell receptors on pig cells are likely to increase the risk of new animal viruses producing human infections [3, 7]. It remains unclear whether these genetically modified pigs will be able to successfully overcome this problem of hyper-acute organ rejection in humans. Nevertheless, there is now great optimism on the part of many proponents of xenografts [2, 18].

There are, however, two other major forms of rejection in which less progress appears to have been made. 'T-cell mediated rejection' is still problematic [1]. This type of rejection with human to human organ transplants remains the major reason for ultimate rejection of human grafts. Conventional immunosuppressive therapy (e.g., cyclosporin, sirolimus) has potent activity that inhibits these T-cell responses. It is not clear however whether these drugs will be equally effective against human T-cell anti-pig responses, as these latter responses appear to be stronger than the T-cell response against human antigens [1].

Probably the most difficult area of graft rejection that does not appear to have been yet overcome is 'delayed graft reaction'. The pathophysiology of this rejection remains unclear [1, 19]. It seems to involve monocytes, natural killer cells, IgG antibody and cytokine activation [1, 19]. Strategies will need to be developed that better target natural killer cells as well as IgG xenograft antibodies. To date, however, there does not appear to be evidence that the problem of 'delayed graft rejection' has been overcome.

Currently therefore, it appears very unlikely that any xeno-organs that are transplanted into humans will survive and function for any prolonged period of time.

3. What factors need to be present for animal viruses to cause disease in people?

There have always been (and will continue to be) viruses that are transmitted from animals to humans by means other than xenografts. Whatever the vehicle for transmission, if a virus (or other microbial agent) in an animal is to cause a problem through xenografts for humans (and in particular to be a public health problem) a number of features will need to be present: 1) the virus (or its genome) must be present in animal cells or tissue; 2) the virus (or its genome) must remain viable in people after transmission of the virus; 3) the virus must be able to replicate in the infected person; 4) the virus will need to be transmissible from person to person.

For an individual to become ill or develop a problem from exposure to an animal virus, at least the first two and usually the first three of these conditions will need to occur. For the problem to become a public health issue (i.e. others other than the recipient are at risk of infection), the fourth criterion will also need to be fulfilled. Obviously the means and rate of transmission will have a major impact on how significant it will be as a public health problem. If it were spread via the respiratory route this would obviously appear to be the most serious means of transmission.

There are many examples (e.g., influenza, HIV) where all four of these criteria have been fulfilled by means other than xenografts [3, 10–12]. This clearly shows that transmission of viruses from animals to humans occurs and that these animal-derived infections can become a 'public health problem'. With xenotransplants there is much less data available because relatively so few of these transplants have occurred in people. Despite the lack of survival of these grafts and limited long-term follow-up, simian cytomegalovirus (CMV) was belatedly shown to have been transmitted to a liver transplant recipient. There is some evidence that suggests this virus may have caused a serious illness in the recipient [20, 21]. Therefore this example with simian CMV shows that the first two criteria have already been fulfilled (see above list). The finding of simian CMV in human leukocytes from the patient suggests also that the virus may have replicated. With other xenotransplants the first two criteria have been fulfilled because there have been many viruses that have been transmitted and have remained viable in the xenotransplant recipients (simian foamy virus, baboon endogenous virus and porcine endogenous retrovirus) [13, 22]. Other indirect evidence to show the potential infection risks associated with xenografts are the many viruses that have been transmitted from monkeys to animal handlers, some of which can persist without apparent symptoms [14] (simian foamy virus) but others which cause serious illness or death [4, 6, 12] (herpes B virus). There has been no person to person transmission of any infection documented to date from xenografts. This may, however, just be a reflection of the small numbers of patients so far studied, the poor survival of these patients as well as poor follow-up [23].

In the only large follow-up study reported to date [22], 160 people were followed after transplantation or exposure to pig tissue for the presence of porcine endogenous retrovirus (PERV). This virus was only relatively recently discovered to be present in the genome of all pig cells and tissues [7, 22]. Many felt that the discovery of PERV would mean that pigs would not be able to be used as donors for xenotransplants [22, 24]. The authors of this report concluded that there was no evidence of transmission of PERV to the recipients of this tissue and that xenografts should therefore proceed [22]. However, their conclusions appear to be inaccurate [25]. Thirty of these patients had PERV detected in their blood. In 23 patients even though they had only very brief exposure to pig tissue (about 30 min during splenic perfusion), pig cells were still detected up to 8.5 years after exposure. While arguable, it therefore appears that the first two conditions (see list) were fulfilled because the PERV genome remained present in a viable form within the viable pig cells that were circulating in these patients [22, 25]. It is not clear though, whether there was active replication of the PERV virus in these patients (i.e. condition 3). Antibodies to PERV were, however, found in a few patients. There were also unexplained illnesses not long after transplantation in others. But so far it has been impossible to determine whether these antibodies were truly reflective of replication of the PERV virus or if they were an artifact. The absence of antibodies, however, does not mean that infection is not present, as pigs themselves do not usually have antibodies against the PERV virus [26] (despite all pigs harbouring the virus). In addition, other infections (such as prions in 'mad cow disease') when transmitted to man from animals are not associated with an antibody response. There were unexplained illnesses seen in some of these patients [22]. However, there may have been other explanations (other than replication of PERV) for these illnesses. This study nevertheless, does highlight the fact that viruses from transplants (in this case PERV) do come across to humans with transplanted cells. This transmission of virus-containing cells occurred even after just short exposure to pig splenic tissue, where the transplantation of pig cells was not designed to occur. Unexpectedly the pig cells (and the viruses they contain) remained viable for many years in the blood in many of the patients [22, 25]. Even if no acute infections were caused in the transplant recipients of this and other smaller studies, we need to remember that many human infections may take decades before they produce disease. Examples of this are the papilloma virus and carcinoma of the cervix, prions and dementia (mad cow disease), hepatitis B and C viruses and hepatoma, and Epstein-Barr virus and lymphomas and nasopharyngeal carcinoma [12]. Given that PERV virus is a retrovirus which has been associated with the production of leukaemia and lymphoma in pigs [27], the absence of disease manifestation after only the relatively short follow-up of many of these patients does not mean that disease could not occur in the future. It could also be argued that even though endogenous viruses such as PERV are in all animal tissues, they will be species specific and therefore unlikely to multiply in new hosts. In vitro experiments have shown, however, that these endogenous retroviruses can grow in

cell lines from different animals as well as a variety of human cell lines [9, 27, 28].

One virus, which appears to have fulfilled all these four criteria (see list) and is associated with the use of animal tissue for medical purposes, is the SV40 virus [16, 29]. In the 1950s and early 1960s, SV40 virus (which is a known oncogenic virus) unfortunately was present in many monkey cell lines and SV40 was transmitted inadvertently to millions of people in polio and adenovirus vaccines [16, 29]. These viruses appeared to be able to replicate and persist in many of the individuals who received these vaccines. The finding of this SV40 virus in other people who had never received the vaccine also suggests that transmission from person to person occurred with these viruses, although it can not be excluded that they acquired the virus from another but as yet unidentified source. Whether this virus has caused disease in the recipients, however, is unclear. The virus has been found in the genome of many tumours (e.g., cerebral tumours) [16, 29]. While it is not clearly established that SV40 is the cause of these tumours, the data at least suggests that there is a reasonable possibility of an association of these tumours with this oncogenic virus.

4. The problem of 'undiscovered' viruses

The SV40 virus highlights the concern held by many about the possibility of the transmission of currently unknown or undiscovered viruses, but nonetheless are present in xenotransplants. Over the last few decades we have frequently found new viruses in animals [3–17]. Many of these viruses have been associated with human disease (e.g., haemorrhagic fever, Menangle, and Nipah viruses). It is also important to note that many common human infections are likely to have been initially derived from animal sources and subsequently human to human transmission became their almost exclusive means of transmission to other people [3–17] (e.g., hepatitis B, HIV). Also of note, relatively recently a number of new viruses have been discovered in pigs (the most likely xenotransplant donor), in particular hepatitis E and the Toro virus [30, 31]. Therefore it is very likely that in all xenotransplants there will be viruses present which are currently unknown and will be associated with disease. One study designed to show the safety of pigs reared for transplantation found no evidence of infection by testing or at necropsy on ten pigs [32]. Unexpectedly, however, they did find that in two pigs (20%) vasculitis was present that involved the heart and kidneys [32]. This had not been detected by any tests while the pigs were alive. If these organs had been transplanted it is unlikely they would have functioned adequately. How do we know that this vasculitis was not due to an as yet unknown virus?

There are also likely to be viruses present (both known and undiscovered viruses) with which there is currently no obvious association with disease but which will be found to cause disease in the future. To put this into perspective and highlight how our knowledge of these subjects is often deficient, we need only look at recent human experience. As little as 10 or 20 years ago many common diseases

were not thought to be associated with infections [12]. Now a clear association has been established for many of these diseases. We now know that if the infective agent is not present, then in many cases the diseases does not occur. *Helicobacter pylori* is associated with peptic ulcer as well as carcinoma of the stomach and lymphoma of the stomach (MALT). Hepatoma is associated with hepatitis B and hepatitis C. T-cell leukaemia is associated with HTLV1. Lymphoma and nasopharyngeal carcinoma are associated with the Epstein-Barr virus. There are also many other common diseases, which may be associated or caused by infective agents (e.g., coronary artery disease and *Chlamydia pneumoniae*). Therefore we must assume that there will be unknown viruses or bacteria transmitted in xenografts which in the future are likely to be associated with infections or conditions but currently for which there is not any clear association (due to our lack of knowledge).

5. What infections from pigs have been transmitted to humans?

Pigs are likely to be the main donor source for xenografts [1–3]. Pigs carry many infections that can cause major problems in humans and then can be (or potentially be) transmitted between humans. New influenza epidemics frequently appear to involve an initial avian source and then spread to humans following recombination in pigs [11, 12]. Hepatitis E appears to have been derived from a porcine source [30]. Parvoviruses are common in pigs [4]. Antibodies to parvoviruses as well as porcine influenza viruses have been found in many of the transplant recipients of porcine islet cells, suggesting potential transmission [5, 33, 34]. Retroviruses present in the genome of all pigs [35] have been transmitted to people through xenotransplants [22, 26]. More recently in Australia and southeast Asia, new forms of a paramyxoviruses have been found that involve pigs [15]. The Menangle virus was found in an area southwest of Sydney and was associated with increased stillbirths in pigs and transmission from pigs to humans. The initial source of the virus is not clear but was most likely bats [15]. The worrisome aspect about this virus is that it was previously unknown. It was transmitted from one species (a bat) to another (the pig). Once in pigs it appeared to be spread by the respiratory route from pig to pig and also was then able to be spread from pigs to humans. What is of even more concern about this virus is that the particular piggery where this virus was found was also the source for xenotransplant material for an experimental animal program in Sydney.

Recently in Malaysia and Singapore there was an outbreak of encephalitis and pneumonic illness in over 200 people with an associated very high mortality [15]. This virus (the Nipah virus) appeared to be transmitted from pig to pig via the respiratory route (there was a very high rate of lung involvement in many of the pigs that died and had post mortems). Many of the people who became ill also had respiratory symptoms.

These paramyxovirus infections (Nipah, Menangle and Hendra viruses) have only been discovered in the last 10 years even though they are likely to have been present

much longer. They have infected humans and in some cases caused severe morbidity and mortality [15]. They are clearly associated with a virus that is transmitted from one animal species to another. What is more worrisome about these examples is that they were transmitted from an animal (usually the bat) which carried this virus asymptotically. It was only when introduced into a new species (usually pigs) that illness occurred (mainly respiratory illness). With the Nipah virus the other major concern is that once introduced into a new species (the pig) it then obviously spread via the respiratory route from pig to pig (and then to humans). This subsequent spread occurred with little or no further involvement of the initial carrier of the virus (i.e. the bat).

6. Longer-term concerns

The recent examples of paramyxoviruses as well as other viral infections reinforce many of the concerns about infection. First, we know that animals carry organisms to which they have adapted without harm, yet when these same organisms jump species, they can become harmful [3–17, 36]. Second, bacteria and viruses mutate and such mutations alter their characteristics [36]. Third, microorganisms co-existing in an environment (such as the human gut) can exchange genetic material with each other [36]. Consequently, it is difficult to predict the consequences of importing animal organs into humans. Such a disease could be unstoppable by any known treatment. Less catastrophic but still frightening scenarios are easy to imagine. Suppose, for instance, that xenotransplantation comes to be accepted, and just a few individuals are eventually infected with an AIDS-like disease that spreads silently in the population until it erupts as a major threat (perhaps untraceable to its original source) dozens or perhaps hundreds of years later.

7. Ethical issues

7.1. Are clinical trials ethical?

The first and central ethical issue raised by these facts is whether it is moral to proceed with research, particularly clinical trials, on xenotransplantation.

It is important to remember that the question facing humanity now is not whether to implant animal organs into humans. Clearly the answer to that question is 'no', as xenotransplantation of tissue or whole organs is not currently a viable treatment. The ethical question is, rather, whether to proceed with further research, including (when immunological hurdles have been surmounted) clinical trials.

The usual answer to the question of whether we should proceed with the research is that because success in xenotransplantation would be the best hope for saving the lives of patients with end-stage organ disease, that research should go forward. The decision is supposed to depend on a calculation juxtaposing number of lives saved with potential risk; it is conceived as a scientific decision, not an ethical one. And, because the lives that might be saved

are very concretely before us, but the possible risks are speculative, proceeding with research is taken to be morally uncontroversial. Those who are not convinced are seen as fear-mongers, blind to the benefits of technology and to human suffering.

However, all these assumptions are questionable. First, the way the problem is framed may have a significant impact on our conception of the solution. Second, ethics needs to counteract the irrational focus on existing sufferers and the failure to imagine the suffering of the statistical individuals who may be put at risk by xenotransplantation. Third, no decision about what to do is merely a scientific decision. Consequently, concerns about the technology need to be taken seriously, not rejected on ad hominem grounds.

7.2. Are xenotransplants the best way to save lives?

Let us start with the empirical issue of whether xenotransplantation truly offers the best hope of saving the lives of patients with end-stage organ disease. Even accepting the current framing of the problem, it seems clear that there are alternatives to xenotransplantation to consider. Certainly, the supply of human organs could be increased by widespread implementation of the most successful programs for increasing donation [37], thorough exploration of creative new ways to encourage donation, live donation, and innovations such as split liver donation. Research on mechanical organs is also advancing. For example, research suggests that in some cases left ventricle assist devices can buy time for some people to heal sufficiently to avoid the need for heart transplant altogether; it is reasonable to expect further progress in the future [38, 39]. In addition, although unlikely to be available for clinical use for many years, 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 xenozoonoses [40–42]. The better use of cells from human cadavers needs to be further explored. Recently human islet cells (from cadaver sources) were directly injected into the portal veins in patients with very unstable diabetes [43]. This resulted in ‘cure’ of their diabetes in all cases at follow-up after 1 year. While these results are still preliminary and required large numbers of cadaver cells, they are much better than results with any porcine islet cell xenotransplants, which have all failed to cure or control diabetes.

Other things being equal, investment in such alternatives would clearly be preferable, given that they are not accompanied by the possibilities of infection inherent in xenotransplant. Although some such work is still in the beginning stages, it might possibly overtake xenotransplantation if the remaining forms of xenorejection prove to be significant scientific obstacles. 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 extending their lives justifies putting so many other lives at risk.

Reframing the problem in terms of a gap between the supply of organs and the need for them opens up still

further the attractive possibility of taking steps 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 behavioural 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 [44, 45]. In addition, intriguing new 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 [45, 46]. Such approaches are preferable for a variety of reasons. First, focusing on them would reduce the need for transplantation, which is expensive and doesn’t necessarily increase quality or length of life [47, 48]. Second, they are desirable on independent grounds, as they would improve general health, not just reduce the need for transplantation [49]. Third, the benefits would be distributed more broadly and in more egalitarian ways. Fourth, this approach could help us rethink our overall technological orientation toward medicine and the reluctance to face our mortality.

These considerations suggest that the standard wisdom about xenotransplantation is simplistic. Making a decision about whether to proceed with research depends on many more factors than comparing the number of lives that might be saved with the potential risk from the technology. Furthermore, decisions about what to do are never mere ‘scientific’ calculations. Facts, by themselves, can never lead to an ethical conclusion: a moral principle, implicit or explicit, is required in order to reach a valid conclusion. Fact-based arguments without such moral principles commit the naturalistic fallacy. Hence, the kinds of objections we are raising to xenotransplantation are legitimate and deserve answers.

7.3. Can we ever obtain proper informed consent and who needs to give it?

The risk of disease transmission raises other, more immediately concrete ethical problems. One question is whether it is possible to obtain informed consent from patients to whom xenotransplantation might be offered. There has been much discussion of the difficulties of getting informed consent from very sick patients whose only hope of survival is experimental therapy. Such patients may grasp at any straw, even if offered with the caveat that it may not help or that it may harm [50]. The US Department of Health and Human Services Office of the Inspector General reinforced the latter point in a recent investigation [51]. This investigation showed that informed consent as a basic requirement has been frequently ignored in drug trials. The media is often used to make it appear that investigational therapy is more promising than it really is [51, 52]. Also, oversight by institutional ethics committees in one city or country can be circumvented by various manoeuvres. With drug trials this is being accomplished by doing increasing numbers of the studies in developing countries, where supervision of many of these aspects can be relatively poor [51]. Most of these questionable approaches have already been documented with xenografts. This includes the performance of a controversial, well-publicized and risky baboon xenograft with little

chance of success and a potential financial conflict of interest by one of the main investigators [53, 54]. There were major doubts on the scientific validity and existence of baboon 'facilitator cells' which were to be resistant to HIV infection and allow engraftment without the development of graft-versus-host disease [53, 54]. Despite the failure of engraftment of any baboon cells, both in the media and in some scientific journals readers were left with the false impression that the transplant may have contributed to the patient's clinical improvement [2, 54, 55]. Financial gain of researchers is also a major issue in inappropriate behaviour in drug trials [51]. Ownership of shares in biotech companies, ownership of patents by researchers and substantial fees paid to investigators to enrol patients are all major issues both in drug trials and xenografts [51, 53, 54].

Serious ethical questions also need to be raised about past and current research in xenografts. It is hard to see how any of the past recipients of solid organs (e.g., heart, liver) could have given informed consent, given that they were all desperately ill, and all transplants resulted in failure and death of the patients. In the recent report promoting xenografts [22], which examined PERV infections, there was no discussion that the majority of patients had undergone a procedure of very dubious medical benefit (i.e. splenic perfusions). Pig spleen perfusions appear to have been performed on many patients in Russia in an unregulated fashion [22, 56]. These were done for a variety of underlying illnesses (e.g., systemic lupus erythematosus, osteomyelitis, abdominal sepsis) despite a lack of convincing data showing that this procedure benefits individuals. It is difficult to believe that it could be useful in so many varied illnesses. Even if there is any benefit, it is likely to be a placebo effect. This has put not only the patient at risk but also those in the wider world community. The increasing use by pharmaceutical companies of developing countries for drug trials to avoid appropriate regulatory supervision [51] suggests this will also be a major issue with xenografts and is likely to get worse.

In general there are serious inconsistencies in the way the research community conceives of work with human subjects and the way patients conceive of it. The research community is well aware that one of the main aims of research is intended to produce new knowledge, and not necessarily improve subjects' welfare. Popular literature intended for patients, however, often suggests that they can get the best care by enrolling in clinical trials [51, 52].

Still more worrisome is the question of who should give consent to such experimentation, and to what. Ordinarily, patients give consent because it is they who bear the risks of treatment. But here, others also bear risk. Should patients, their health care providers, and family intimates also be required to give consent before proceeding? Must they agree to possible future quarantine if a zoonotic infection develops? What if some refuse or simply are noncompliant if infection develops? Are proponents of xenotransplantation prepared to envision involuntary quarantine, if possibly infected individuals can be traced? [3, 50, 57, 58]. The debate thus far on these important issues has been relatively limited [5, 58–62]. Before going forward with xenotransplantation, there needs to be full and

public discussion of these issues and a satisfactory resolution of them.

7.4. Issues of social equity

These questions about social risk are magnified by the fact that xenotransplantation might become available only within the confines of private medicine. It is expected to be expensive, and thus many people will not be able to afford it, even though everyone will be at risk of infection. This injustice is still more troubling to the extent that public resources are being mobilized to develop xenotransplantation. And although this issue is not entirely new in modern medicine, xenotransplantation raises it in an exceptionally stark way because everyone, not just recipients, are potentially at risk because of the potential transmission of disease.

7.5. Animal rights and welfare

While not unique to the issue of xenotransplantation, the use of animals for this purpose raises two major issues. First can they be protected from suffering while they are alive and when they are killed? Second, is it morally acceptable to alter their genome to make xenotransplantation possible? It is unlikely that concerns about them can be addressed adequately in just the medical research environment, where there is an assumption that human welfare always prevails over animal welfare. Nonetheless, concern about animals remains part of the overall picture in xenotransplantation, and this concern is relevant to any final overall assessment of whether to proceed with research or instead to pursue alternative approaches to the problem to which it responds.

8. Conclusion

What if we were trying to design the ideal experiment in which a new virus that would infect humans would be cross-transmitted from pigs to humans? We would be hard pressed to come up with a better experiment than what is planned to be done with xenografts (and on a massive scale). Currently there are plans for large numbers of genetically engineered pigs to be developed whose outer cell membranes will be altered so they more closely mimic the antigens found on human cells. Any new animal viruses that multiplied would therefore likely be covered in human antigens rather than porcine antigens. Organs (and the viruses they contain) from these pigs will then be transplanted directly into normally sterile sites, bypassing important barriers in humans that protect us from animal viruses (e.g., intact skin and intestinal mucosal surfaces). These patients will also be very heavily immunosuppressed. This will mean that even if some of these animal viral antigens are recognised, the probability of the virus being destroyed will be significantly compromised.

From the social perspective, can we afford to proceed with research on xenografts, given that there are risks that devastating infections may occur not only in the individual who receives the transplant but also in the general community? From the individual transplant recipient perspective, would it not clearly be unethical to proceed with

clinical trial of whole organs as we know these transplants are not currently a viable successful treatment option? Long-term survival of these transplant organs does not even occur consistently in experimental animals, let alone in humans. The life expectancy of any of these transplant recipients will therefore be lower than if they had remained on human transplant waiting lists. Thus far these questions have not been satisfactorily answered. Facilities and legislation are not in place to cope with a disaster, should it occur. If not a ban, then at least a moratorium on xenografts needs to be in place until at least all these issues are satisfactorily addressed.

In summary, the ethical concerns about xenotransplantation, thus far from mere obstructionism or moral blindness, deserve far more careful consideration than they have received. There is a serious risk that xenotransplantation would do more harm than good. Because the resolution of the ethical and scientific obstacles to xenotransplantation is not guaranteed, we need to consider whether resources now being directed to it would be better deployed elsewhere. It is also arguable that alternative approaches could reasonably be expected to help suffering patients with less risk both to themselves and to humanity as a whole. Some approaches could, in addition, help reorient our attention away from medicine and toward a broader focus on the prerequisites for health. Only such a reorientation will, in the long run, reduce the burden of disease and disability.

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