

Xenotransplantation—2000

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Major advances in techniques and the development of new immunosuppressive drugs and strategies have led to transplantation becoming the treatment of choice for end stage organ failure, with patients achieving long term survival and a high quality of life. The cost benefits of transplantation have been well recognised and renal transplantation alone saves huge amounts of money spent on dialysis.¹ Despite the many advantages of organ transplantation, this treatment is unavailable to many who would benefit, owing to the shortage of organs. The gap between the numbers on waiting lists and the available organs continues to widen as the number of donors declines in many countries.² The unmet need for organs may be still higher, as transplant physicians are selective about who they list because of the lack of donors, and the potential need for transplantation may exceed availability even if all suitable organs were used.

The shortage of human organs for transplantation has stimulated intense research into alternative sources. Consideration has been given to the use of old world monkeys and apes, but the need to rear the animals in isolation raises ethical concerns. In addition, viruses from non-human primates are perceived as a particular risk to humans. Pigs are currently the only animals being seriously considered as a source of organs for transplantation to humans. Pigs have been domesticated and have lived close to man for hundreds of years, grow quickly to a suitable size, produce large litters, can be reared in specific pathogen-free conditions, and there is already considerable expertise in pig husbandry. The ethical concerns are less, given that animals are reared for human consumption and porcine tissues are already used in prosthetic heart valves.

Xenotransplantation (the transplantation of tissues from one species to another) has several potential benefits provided the various obstacles can be overcome. The use of pigs as a source of organs would provide an almost unlimited supply. The organs would be available at all times, allowing surgery to be planned and optimally timed, and the damaging effects of brain death on the organs would be avoided.^{3,4} Early work on xenotransplantation showed that the major obstacle would be the immune reaction of the host to the graft. Recent advances, however, have made significant strides in overcoming this, bringing the possibility of xenotransplantation closer. If the problems of rejection can be overcome, there remain concerns that there may be physiological or anatomical incompatibilities or limitations that affect graft function or survival. There are particular concerns that the xenograft may allow the cross species transfer of

infectious organisms and allow spread to other members of society.

A further advantage of the pig is that it is possible to manipulate the germline DNA in order to insert human genes, allowing pig tissues to be better tolerated by human recipients.⁵ There are also considerable similarities between porcine and human anatomy and physiology. However, a recent comparison of the anatomy of porcine and human hearts identified several differences, many of which are attributable to the different stances (walking on four legs rather than two; unguigrade versus orthograde) and the effect of gravity on the development of the heart.⁶ Despite these differences, the transplanted organs appear to be able to adapt very well to a new host, for example pig hearts in monkey hosts.⁷

Physiological differences may also pose problems. While the handling of sodium and potassium by pig and human kidneys is similar, there are differences in the normal serum concentrations of calcium and phosphate. These simple metabolic incompatibilities may not be of great significance, but multicellular organisms also require cells to be able to communicate with each other through hormones and other molecules, and little is known about these more complex cross species compatibilities.⁸ Porcine insulin has been in use for many years as a treatment for diabetes mellitus and is clearly compatible, differing by only one amino acid from human insulin. During insulin production, C peptide is released and there is evidence that it has biological activity. In a rat model, human and rat C peptide have been shown to prevent or attenuate some diabetes induced pathophysiological changes.⁹ Porcine C peptide differs considerably from human C peptide and may not have this effect.⁸ In contrast, erythropoietin appears to be ineffective in the pig to monkey transplant model but this may be overcome with replacement therapy.¹⁰ These problems will vary depending on which organs are transplanted but are likely to be most marked in the liver owing to the multiple synthetic functions of the organ. The efficacy of porcine complement and coagulation proteins in humans is not known, and furthermore, significant structural differences may render them immunogenic. Many of the inflammatory and immune reactions that will involve the graft will depend on adhesive interactions between porcine endothelium and inflammatory cells. An incompatibility might work to the graft's advantage if immune cells are unable to adhere and transmigrate, but the converse—pig haematopoietic cells unable to adhere to human endothelium—could prevent strategies aimed at inducing tolerance.¹¹ The full spectrum of physiological incompatibilities

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is not yet clear, but differences may be amenable to other treatments and should not be an insurmountable barrier.

Discordant xenografts are those rejected within minutes to hours of perfusion by recipient blood, a process termed hyperacute rejection.¹² This rejection is caused by the presence of naturally occurring preformed xenoreactive antibodies which account for 2–4% of circulating immunoglobulin. The antibodies bind mainly to the Gal α 1-3Gal epitope, which is widely present in the animal kingdom but absent in humans, higher primates, and old world monkeys.¹³ Binding of antibody to endothelium results in complement activation with endothelial damage, oedema, haemorrhage, and graft loss. Deposition of antibody, predominantly IgM, and terminal complement components can be identified, using immunohistochemical techniques, on the endothelial surface of the graft.¹⁴ The grafts function as though there has been a complete failure in the integrity of the endothelial barrier. Although complement mediated lysis of endothelial cells would account for this, there is little evidence of endothelial cell destruction. Complement can mediate other changes in the endothelium, most importantly the shedding of heparan sulphate from the endothelial cell surface,¹⁵ changes in cell shape resulting in the formation of intercellular gaps, and the expression of P-selectin on the cell surface, which can serve as a ligand for platelets.¹⁶

Major advances have been made in overcoming the problems of hyperacute rejection. Immunoabsorption of the antibody¹⁷ or depletion of complement by the use of cobra venom factor or soluble complement receptor 1 (sCR1) results in improved graft survival and prevents hyperacute rejection.^{18–20} The longest survival, however, has been achieved by the use of genetically modified transgenic pigs carrying and expressing human complement regulatory proteins CD55 (decay accelerating factor, DAF), CD46 (membrane cofactor protein, MCP), and CD59 (protectin), either singly or in combination.^{7 10 21 22}

If hyperacute rejection is prevented, the grafts become subject to acute vascular xenograft rejection or, as it is also called, delayed xenograft rejection. This is characterised by endothelial damage and swelling, thrombosis, and ischaemia. A variable cellular infiltrate may also be observed.²³ Continued interaction of the graft with xenoreactive antibodies appears important in the process. Peak levels of xenoreactive antibodies are seen at the time of rejection, and strategies that remove antibodies or inhibit their synthesis have been shown to delay the onset of acute vascular rejection.^{24 25} Complement also almost certainly has a role. Acute vascular rejection may occur in complement depleted animals, as depletion strategies are not 100% effective and low level complement activation is sufficient to stimulate a procoagulant and proinflammatory change in the endothelial cells.^{26 27} The primary interface of the graft and host is the endothelial cell barrier and this has a crucial role in regulating coagu-

lation and leucocyte trafficking in tissues. Exposure of endothelial cells to inflammatory mediators results in their activation, with a dramatic change in their function.^{28 29} Activated endothelial cells change from an anticoagulant to a procoagulant phenotype with loss of thrombomodulin and heparan sulphate, although porcine thrombomodulin has been shown to be a poor regulator of the human coagulation cascade. The endothelial cells also synthesise tissue factor which is able to initiate coagulation by binding coagulation factor VIIa. The balance of the fibrinolytic pathway is shifted by decreased production of plasminogen activators and increased synthesis of plasminogen activator inhibitor-1.³⁰ The endothelial cells become proinflammatory owing to the increased expression of cell adhesion molecules such as E-selectin (E-Sel), and vascular cell adhesion molecule (VCAM).³¹ These phenotypic changes can be induced by the activation of complement on the surface of endothelial cells. This is not a direct response of the endothelial cells but requires the synthesis and secretion of interleukin (IL)-1 α by the endothelial cells, which activates the cells in an autocrine fashion. This complement mediated activation of endothelial cells can be blocked by the use of IL-1 receptor blockade or anti-IL-1 α antibodies.²⁷

Many of the key synthetic events that underlie endothelial activation require gene transcription. Many of the genes are to a large extent dependent on the actions of the transcription factor NF- κ B. This transcription factor is usually present in the cytoplasm of cells complexed to its inhibitor I κ B α . On receiving an activating stimulus, the NF- κ B is released and translocates to the nucleus where it is able to bind to promoter regions, resulting in transcription.³² This common pathway of activation may provide a site for therapeutic intervention to inhibit endothelial cell activation.

Cellular mechanisms may also play a role in rejection. Natural killer cells have been observed in some grafts with acute vascular rejection, and the presence of IgG in the graft may aid in the recruitment and activation of these cells. Natural killer cells are able to directly recognise oligosaccharide ligands expressed by endothelial tissues³³ and have been shown to cause morphological changes and activation of endothelial cells in vitro, thereby contributing to acute vascular rejection.^{34–36} Macrophages have also been observed within grafts and are a potential source of inflammatory cytokines such as tumour necrosis factor α , which is also an endothelial cell activator.^{37 38}

Elicited cellular immune responses occur following xenotransplantation but it is not clear whether these differ from the response seen in allotransplantation and whether novel immunosuppressive strategies will be needed. The vigorous nature of the humoral response to xenografts has made it difficult to study the nature of the cellular response because of short graft survival and the high level of immunosuppression required to overcome the humoral response. Studies of free tissue grafts, such as pancreatic islet cells, which are non-

vascularised have suggested a role for CD4 cells. In mixed leucocyte cultures, T cells tend to show a poor direct response to xenogeneic cells. This is occurring in the absence of antigen presenting cells and is thought to reflect impaired interaction with xenogeneic major histocompatibility complexes,³⁹ and indirect responses may be of more importance.

Experience in human allotransplantation has shown that the donor organ can be a source of a wide variety of infectious agents. These include viruses such as cytomegalovirus, Epstein-Barr virus, and HIV, parasites such as *Toxoplasma gondii*, a wide range of bacteria including mycobacteria, and even fungal infections. The results of these can be devastating, threatening the survival of the graft and the life of the patient.⁴⁰ The fact that these adverse events are now relatively rare reflects the careful approach taken in selecting the donor and reducing opportunities for transmission or contamination at organ procurement. This experience has focused attention on the need to assess the risk of infection from the source animal used for xenotransplantation.

The organisms that may pose a risk to the human recipient need to be identified. It is misleading to consider only the known zoonotic agents of pigs, even if that is extended to those reported to cause infection in an immunocompromised patient. In xenotransplantation, the classical route of acquisition of most zoonoses has been bypassed, and the practical risk of infection being introduced with the graft must be considered. *Cryptosporidium*, for example, causes severe disease in the immunocompromised patient and can be found in the stool of a pig. It would be unlikely to reach a human recipient by way of the transplanted organ unless gut transplantation were considered. Conversely some pig agents never thought of as zoonotic could be introduced with an infected pig organ. It is known that a wide variety of bacteria, including environmental organisms and plant pathogens, as well as saprophytic fungi can infect the immunocompromised host. There is not therefore the same species specificity as is seen in many viral infections. Parasites may appear host specific, but direct introduction with porcine tissue into an immunosuppressed host may lead to diseases not previously encountered.

An infection acquired at xenotransplantation (xenozoonosis or xenosis) may therefore occur when an organism of low host specificity reaches man by direct inoculation with the organ at surgery. Alternatively, species specific organisms may reactivate in the porcine graft, particularly when the human host is immunosuppressed. Thirdly, a previously species specific organism may change in the new host environment to become a human pathogen.⁴¹

The insertion of human complement regulatory proteins into pig cells has caused some concerns. Many animal viruses with lipid envelopes are sensitive to human serum. Some of the antiviral effect is mediated by complement. This has been observed with mammalian C type retroviruses and may prevent transmission of such retroviruses from animals to humans.

Lysis of the viruses is by complement activated by the binding of anti- α -Gal antibodies to the viral membrane.⁴² Virus inactivation can therefore occur by the same mechanism as hyperacute rejection. If the α -Gal antibodies are removed or production suppressed then lysis will not occur. Incorporation of complement regulatory proteins into the viral envelope could render the virus resistant to complement mediated lysis. This may increase the likelihood of viral zoonosis in the setting of xenotransplantation. The complement regulatory proteins also function as receptors for some other viruses. CD46 is a receptor for the measles virus⁴³ and CD55 for certain echoviruses and coxsackie viruses.^{44 45} Transgenic animals may therefore become susceptible to human viruses and, conversely, previously species specific porcine viruses may be able to adapt to use the human proteins as viral receptors.⁴⁶

Much is known about the infectious agents present in domesticated pigs, but new diseases are being recognised.⁴⁷ Identified pathogens can be excluded from animals reared as specifically pathogen free.^{48 49} The logistical problems and detrimental effects on growth of rearing pigs in a totally germ-free environment makes this a less attractive option. As herds will be raised specifically for the purpose of organ supply, it should be possible to institute a programme of disease prevention and screening from the outset. This would have to be modified as knowledge of pig infection advances.⁵⁰

While many of the potential pathogens can be screened for and eliminated from herds reared under specific pathogen-free conditions, pigs, like all mammals, have retroviruses within their genomic DNA. These proviral genomes are inherited in a Mendelian fashion. These viruses show some sequence homology with other retroviruses which are known to cause disease such as feline leukaemia virus. It is estimated that there are approximately 50 endogenous retroviral copies in most pig chromosomes. It is unlikely that it will be possible, through either selective breeding or gene knockout technology, to exclude these sequences. Concerns have been raised that retroviruses can reactivate and pose a threat to the recipient. It has recently been shown that retroviruses released from porcine endothelial cells are capable of infecting human cells in tissue culture.^{51 52} Analysis of human patients who have been exposed to porcine tissues, either through islet cell grafts⁵³ or through connection to extracorporeal circuits to pig kidneys⁵⁴ or livers, has not shown any evidence of infection, either serologically or by the demonstration of DNA sequences from the porcine retroviruses.^{55 56} These studies are limited, however, in that few patients were immunosuppressed and the porcine tissues were not from transgenic animals.

The risk of infection following xenotransplantation seems small but is still difficult to predict. By breeding and rearing animals free of a defined list of organisms there is the potential to produce an organ donor where the risks are less than those from a previously

unknown human donor. The emphasis has been on looking at the risk of viral infection, in particular the problem of endogenous retroviruses. It should, however, always be borne in mind that the other organisms that may be transmitted at transplantation can cause major problems. Care must be taken, not only in the development of the specific pathogen-free animal, but also during organ procurement, transport, and transplantation to ensure that transmission of infection that could have been avoided does not occur. The decision to progress to clinical trials of xenotransplantation will need to balance the benefit to the individual with any potential risk to society.⁵⁷

The concerns over anatomical and physiological disparity do not appear insurmountable. The risks of zoonosis, particularly in relation to retroviruses, appear small but remain an area of concern. The increased understanding of the immunopathology of xenograft rejection and the development of new immunosuppressive strategies bring the possibility of clinical xenotransplantation closer.

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