POSITION PAPER

Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: The Present Status of Xenotransplantation and Its Potential Role in the Treatment of End-Stage Cardiac and Pulmonary Diseases

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1.0. SUMMARY

An urgent and steadily increasing need exists worldwide for a greater supply of donor thoracic organs. Xenotransplantation offers the possibility of an unlimited supply of hearts and lungs that could be available electively when required. However, antibody-mediated mechanisms cause the rejection of pig organs transplanted into non-human primates, and these mechanisms provide major immunologic barriers that have not yet been overcome. Having reviewed the literature on xenotransplantation, we present a number of conclusions on its present status with regard to thoracic organs, and we make a number of recommendations relating to eventual clinical trials.

Although pig hearts have functioned in heterotopic sites in non-human primates for periods of several weeks, median survival of orthotopically transplanted hearts is currently <1 month. No transplanted pig lung has functioned for even 24 hours. Current experimental results indicate that a clinical trial would be premature. A potential risk exists, hitherto undetermined, of transferring infectious organisms along with the donor pig organ to the recipient, and possibly to other members of the community. A clinical trial of xenotransplantation should not be undertaken until experts in microbiology and the relevant regulatory authorities consider this risk to be minimal.

A clinical trial should be considered when ap-

proximately 60% survival of life-supporting pig organs in non-human primates has been achieved for a minimum of 3 months, with at least 10 animals surviving for this minimum period. Furthermore, evidence should suggest that longer survival (>6 months) can be achieved. These results should be achieved in the absence of life-threatening complications caused by the immunosuppressive regimen used. The relationship between the presence of anti-HLA antibody and anti-pig antibody and their cross-reactivity, and the outcome of pig-organ xenotransplantation in recipients previously sensitized to HLA antigens require further investigation. We recommend that the patients who initially enter into a clinical trial of cardiac xenotransplantation be unacceptable for allotransplantation, or acceptable for allotransplantation but unlikely to survive until a human cadaveric organ becomes available, and in whom mechanical assist-device bridging is not possible.

National bodies that have wide-reaching government-backed control over all aspects of the trials should regulate the initial clinical trial and all subsequent clinical xenotransplantation procedures for the foreseeable future. We recommend coordination and monitoring of these trials through an international body, such as the International Society for Heart and Lung Transplantation, and setting up a registry to record and widely disperse the results of these trials.

Xenotransplantation has the potential to solve the problem of donor-organ supply, and therefore research in this field should be actively encouraged and supported.

2.0 ABBREVIATIONS

ARDS, acute respiratory distress syndrome (acute non-infectious lung failure)
COPD, chronic obstructive pulmonary disease
ECMO, extracorporeal membrane oxygenation
HTx, heart transplantation
ISHLT/UNOS, International Society for Heart and Lung Transplantation/United Network for Organ-Sharing
LTx, lung transplantation
PPH, primary pulmonary hypertension
UK, United Kingdom
UNOS, United Network for Organ Sharing
US, United States of America
XTx, xenotransplantation

3.0 INTRODUCTION

In August 1999, the president of the International Society for Heart and Lung Transplantation (ISHLT), Robert Kormos, set up a Xenotransplantation Advisory Committee charged with drawing up a white paper on the present status of xenotransplantation (XTx) and its potential role in the future of treating patients with end-stage cardiac and pulmonary diseases. The committee, which included members from a wide geographic background as well as diverse professional interests, has considered this topic in a global context. In particular, members considered the need for a new source of thoracic organs for transplantation; the potential of XTx to fulfill this need in comparison with other therapeutic modalities; the immune barriers and potential complications of clinical XTx; as well as some of its ethical, regulatory, and financial aspects. We considered the results we believe necessary in experimental models before progression to a clinical trial should be undertaken, the criteria for patient selection for the initial clinical trials, and the results necessary in the clinical trials to further pursue this field of therapy. Finally, we assessed whether the state of the science was adequate at this stage to initiate a clinical trial, what regulatory mechanisms would be advisable to oversee such a trial, and who or what body should financially support such a trial. We would emphasize that the field of XTx research, particularly that involving thoracic-organ transplantation, should be reviewed at intervals and revisions made to our conclusions and recommendations.

4.0 NEED FOR MORE ORGANS AND POTENTIAL FOR THORACIC-ORGAN TRANSPLANTATION

After reviewing available data on donor thoracic-organ availability in the United States, Europe, and several other countries (see Section 14.0 Appendix 1), we conclude that even with the present rigorous selection criteria for patients submitted for heart, lung, or heart–lung transplantation, a definite need exists for a new source of thoracic organs, and that this need is universal in all countries that perform these procedures. Furthermore, a new source would allow, and be followed by, considerable expansion in thoracic-organ transplantation procedures, and might enable heart transplantation (HTx) and/or lung transplantation (LTx) in some countries that now either do not offer this form of therapy or offer it only rarely.

5.0 POTENTIAL APPROACHES TO THORACIC-ORGAN DONOR SHORTAGE

Table I lists potential approaches to alleviating the thoracic-organ donor shortage; these also are briefly discussed in Appendix 2 (Section 15.0). Increased number of available human cadaveric donor thoracic organs, anticipated improvements in medical

TABLE I Potential approaches to alleviating thoracic-organ donor shortage

1. Increased supply of human cadaveric organs
2. Improved medical care of patients with end-stage cardiac or pulmonary disease
3. Use of sub-optimal donor organs
4. Use of living donor organs (lung)
5. Implantable mechanical assist devices
6. Alternative surgical procedures for advanced cardiac or pulmonary disease (e.g., mitral valve repair for cardiomyopathy, lung volume reduction surgery for COPD)
7. Gene therapy (e.g., for arteriosclerosis/cystic fibrosis)
8. Cellular augmentation of the myocardium/tissue engineering
9. Xenotransplantation

therapy, and alternative surgical procedures (e.g., mitral valve annuloplasty for dilated cardiomyopathy or lung volume reduction for chronic obstructive pulmonary disease [COPD]) may make a small impact on the balance between supply and demand in thoracic-organ transplantation. Nevertheless, many thousands of patients will require some form of thoracic-organ replacement. Approaches that involve gene therapy, cellular augmentation, and tissue engineering are in very primitive states of development. Further developments in implantable mechanical devices, or major advances in XTx represent the most likely solutions to cardiac replacement in the medium term. Despite the current primitive state of lung XTx, it offers a potential solution to treating patients with end-stage pulmonary disease, although presently far from achieving this goal.

6.0 XENOTRANSPLANTATION—PRESENT POSITION

6.1 Clinical Experience

Both non-human primates and domesticated mammals have been used as sources of hearts for transplantation into humans (Table II).[1,2] In the first heart transplantation performed in a human (in 1964 in Mississippi) James Hardy and his colleagues used a chimpanzee heart.[3] They deemed the heart insufficient in size to support the patient's circulation, and the patient died on the operating table approximately 1 hour after the procedure ended. In 1968, Ross and his colleagues[4,5] transplanted a pig heart and Cooley and colleagues[6,7] transplanted a sheep heart into humans. Both organs were hyperacutely rejected immediately after revascularization. In 1969, surgeons in France transplanted another chimpanzee heart, without success.[8,9]

Barnard et al[10] carried out heterotopic HTx using a chimpanzee heart and a baboon heart in 2 separate patients who had undergone open-heart valve surgery and in whom cardiopulmonary bypass could not be discontinued because of inadequate function of the native hearts. The chimpanzee heart functioned 4 days before it underwent antibody-mediated rejection, and the baboon heart failed within hours from a combination of inadequate size and probable antibody-mediated rejection.

In 1984, following the introduction of cyclosporine as an immunosuppressive agent, Bailey and his colleagues transplanted a baboon heart into an infant (Baby Fae). The heart functioned 20 days before being rejected by an antibody-mediated mechanism.[11] Reports exist of 2 more pig heart transplants: in Poland[12] and in India (unpublished) in 1991 and in 1996, respectively, but neither heart functioned more than 24 hours.

No attempts have been made at clinical lung XTx.

6.2 Choice of Source Animal

The limited number of primates available as organ donors for humans, the limited size of those that are available in relatively large numbers (e.g., baboons), the potential risk of transferring infection, particularly viral, and the ethical considerations of using such animals as donors for humans on a large scale, as well as several other considerations, preclude using non-human primates in this role (Table III).[13,14]

Pigs are suitable sources of organs for humans in many respects and have certain advantages over other mammals for this role (Table III).[15–17] Therefore the discussion of XTx that follows will consider only the pig as the organ source.

6.3 Immunologic Barriers

The immunology of XTx has been the focus of intensive study during the past decade, and several authors have reviewed it.[18–21] Here we will mention only a brief outline of barriers to successful XTx.

Currently, 4 major immunologic barriers exist to XTx, namely, hyperacute rejection, acute vascular rejection, acute cellular rejection, and chronic rejection. Of these, hyperacute rejection can be prevented by currently available techniques. Acute vascular rejection can be delayed but not prevented. Data on prevention of acute cellular rejection is inconclusive. Virtually nothing is known about the development of chronic rejection and its susceptibility to prevention by immunomodulation.

The presence of anti-pig antibodies directed against α1,3galactose (Gal)[22–27] (and possibly oth-

TABLE II World experience in clinical heart xenotransplantation

Case	Year	Surgeon	Institution	Donor	Type of transplant	Outcome	Reference source
1	1964	Hardy	University of Mississippi, Jackson, Mississippi, USA	Chimpanzee	OHT	Functioned 2 hours (heart too small to support circulation)	(3)
2	1968	Ross	National Heart Hospital, London, UK	Pig	HHT	Cessation of function within 4 minutes (? vascular rejection)	(4, 5)
3	1968	Ross	National Heart Hospital, London, UK	Pig	Perfused with human blood but not transplanted	Immediate cessation of function (? vascular rejection)	(4, 5)
4	1968	Cooley	Texas Heart Institute, Houston, Texas, USA	Sheep	OHT	Immediate cessation of function (? vascular rejection)	(6, 7)
5	1969	Marion	Lyon, France	Chimpanzee	? OHT	Rapid failure (? raised pulmonary vascular resistance)	(8, 9)
6	1977	Barnard	University of Cape Town, Cape Town, South Africa	Baboon	HHT	Functioned 5 hours (heart too small to support circulation)	(10)
7	1977	Barnard	University of Cape Town, Cape Town, South Africa	Chimpanzee	HHT	Functioned 4 days (failed from probable vascular rejection)	(10)
8	1984	Bailey	Loma Linda University, Loma Linda, California, USA	Baboon	OHT	Functioned 20 days (failed from vascular rejection)	(11)
9	1991	Religa	Silesian Academy of Medicine, Sosnowiec, Poland	Pig	OHT	Functioned <24 hours	(12)
10	1996	Baruah	India	Pig	OHT	Functioned <24 hours	Unpublished

Source: Taniguchi S, Cooper DKC.[2]
OHT = orthotopic heart transplantation
HHT = heterotopic heart transplantation

er)[22,28–30] epitopes on pig vascular endothelium leads to immediate or early antibody-mediated (hyperacute) rejection when these organs have been transplanted into humans or Old World non-human primates.[31–38] A number of methodologies can now be used to overcome hyperacute rejection of the pig heart, but the pig lung seems more susceptible to this response.[30,33–36,38–43] Therapeutic modalities that protect against hyperacute rejection include depletion or inhibition of the recipient's anti-pig (anti-Gal) antibodies[23,30–33,35,41,44–59] or of complement,[49,60–63] the use of organs from pigs genetically engineered to provide protection against human complement by the introduction of transgenes for one or more human complement regulatory proteins,[38,42,64–83] and several other modalities.[84,85]

However, despite intensive immunosuppressive therapy, a delayed form of antibody-mediated rejection, known as acute vascular rejection or delayed xenograft rejection, develops within days or weeks.[86–91] Although the mechanism of acute vascular rejection remains uncertain, it appears to be antibody-mediated (possibly through antibody-dependent, cell-mediated cytotoxicity), but the contribution of complement activation is less certain.

Intensive work into overcoming this barrier continues at several centers and involves a number of different approaches that include attempts to induce "accommodation" (lack of injury to the porcine endothelial cells despite the presence of normal levels of both antibody directed against specific porcine antigens and complement).[92,93] Researchers also are exploring genetic engineering and nuclear transfer techniques to modify the antigen expression

TABLE III Relative advantages and disadvantages of baboons and pigs as potential sources of organs and tissues for humans

	Baboon	Pig
Availability	Limited	Unlimited
Breeding potential	Poor	Good
Period to reproductive maturity	3–5 years	4–8 months
Length of pregnancy	173–193 days	114 ± 2 days
Number of offspring	1–2	5–12
Growth	Slow (9 years to reach maximum size)	Rapid (adult human size within 6 months)[b]
Size of adult organs	Inadequate[a]	Adequate
Cost of maintenance	High	Significantly lower
Anatomic similarity to humans	Close	Moderately close
Physiologic similarity to humans	Close	Moderately close
Relationship of immune system to humans	Close	Distant
Knowledge of tissue typing	Limited	Considerable (in selected herds)
Necessity for blood-type compatibility with humans	Important	Probably unimportant
Experience with genetic engineering	None	Considerable
Risk of infection transfer (xenozoonosis)	High	Low
Availability of specific pathogen-free animals	No	Yes
Public opinion	Mixed	More in favor

Source: Cooper DKC, Lanza RP.[21]
[a]The size of certain organs, e.g., the heart, is inadequate for transplantation into adult humans.
[b]Breeds of miniature swine are approximately 50% of the weight of domestic pigs at birth and sexual maturity, and reach a maximum weight of 200–300 lb (<130 kg).

of pig tissues and to render them less susceptible to the effect of antibody.[94–100] Some encouraging progress has recently been made in preventing an induced antibody response to pig antigens with costimulatory blockade,[101] but to date it has not proved possible to conclusively prevent development of acute vascular rejection. Potential approaches to overcoming this barrier include suppression of antibody production with monoclonal antibodies and immunotoxins directed against B and plasma cells, particularly those that produce Gal-specific antibodies, and the induction of B-cell tolerance (see below).

In the pig-to-baboon or pig-to-cynomolgus monkey models, acute vascular rejection has developed in all xenotransplanted hearts except in some animals that required euthanasia or died from concomitant complications, usually related to intensive immunosuppressive therapy.[65,76,77,80,90] Acute vascular rejection has sometimes been associated with development of disseminated intravascular coagulation.[48,82,102,103]

If antibody-mediated rejection could be prevented, we anticipate an acute cellular response will develop, similar to that seen in allotransplantation.[104–108] Current evidence suggests that the intensity of this response will be at least equal to that elicited toward an allograft, and may well be greater. It remains uncertain whether currently available immunosuppressive drugs can control this response. It is also likely, although hitherto undetermined, that chronic rejection will develop early and be severe and that, even if the initial antibody-mediated and cellular responses can be suppressed, graft function may fail because of chronic rejection at a relatively early stage relative to an allograft. (This will be offset to some extent by the availability of organs for retransplantation.) We stress that experimental data on the development of acute cellular rejection and of chronic rejection remain extremely limited. Solutions to these barriers lie in the realm of improved immunosuppressive therapy or tolerance induction. When a pig is the organ source, however, it is possible to avoid non-immunologic insults to the donor organ at the time of excision and transplantation, e.g., the detrimental effect of brain death and of prolonged cold-ischemic time. This may contribute to decreased incidence of late graft dysfunction/chronic rejection.

It is not within the confines of this paper to detail these rejection responses or to detail the approaches being made to overcome them. These have been described in many other publications, some of which have been referenced above. However, at the

TABLE IV Recent experimental trials of orthotopic cardiac xenotransplantation in the pig-to-baboon model[a]

Donor pig	Immunosuppressive regimen	*n*	Survival (days)	References (year)
hDAF	CPP, CYA, CS	10	<1–9 (median 2)	76 (1998)
hDAF	Induction CPP, CYA, MMF, CS	6	<1–39 (median 12)	109 (1999)

[a]For a detailed review of previous experimental studies of xenotransplantation in the pig-to–non-human primate model see Lambrigts et al.[33]
CPP, cyclophosphamide; CS, corticosteroids; CYA, cyclosporine; hDAF, pig transgenic for human decay–accelerating factor; MMF, mycophenolate mofetil.

present time, the longest survival of a pig heart in a non-human primate in the heterotopic (non–life-supporting) site is 99 days (median, 26 days),[65] and in the orthotopic site is 39 days (median, 12 days) (Table IV). [76,90,109] Despite investigation of numerous immunosuppressive regimens, this limited survival indicates that immune barriers have not yet been overcome.

The Imutran group in Cambridge, UK, have performed 2 series of orthotopic HTx using hearts from pigs transgenic for the human complement-regulatory protein, decay-accelerating factor (hDAF) (Table IV). In the first series of 10 transplants, researchers achieved a maximum survival of 9 days (with a median survival of 2 days) using an immunosuppressive regimen consisting of cyclophosphamide, cyclosporine, and corticosteroids.[76] In a second series of 6 transplants, immunosuppression consisted of a short induction course of cyclophosphamide followed by maintenance therapy with cyclosporine, mycophenolate mofetil, and corticosteroids.[90,109] The maximum survival was 39 days, with median survival of 12 days. The recipient of the longest-surviving graft was active and energetic throughout its post-operative course and remained free of signs of cardiopulmonary failure. Although the circumstances of death remain uncertain, death did not appear to be related to graft rejection. These results confirmed that a well-functioning pig heart can sustain life in a non-human primate.

No data report survival beyond a few hours following pig LTx in non-human primates.[38,69,79] Furthermore, recipients in these experiments remained anesthetized while researchers assessed function of the unilateral pig LTx. To date, therefore, no non-human primate has regained consciousness or been actively supported only by a pig lung.

Of note, the results of life-supporting kidney transplantation in the hDAF pig-to–non-human primate model are better than those of orthotopic HTx, and comparable with that of heterotopic HTx in this model. Currently, recipient survival is approximately 2 to 70 days, with a median of approximately 30 days, the exact results depending on the immunosuppressive regimen used.[33,77,80,110] The best results have been obtained in cynomolgus monkeys that had undergone splenectomy and received maintenance therapy with cyclophosphamide, cyclosporine, and corticosteroids.[33,111] Maximal survival was 78 days, with a median of 39 days. Two of 9 animals developed lymphoproliferative disease.

More recently, splenectomized cynomolgus monkeys received induction therapy with cyclophosphamide, and maintenance therapy with cyclosporine, a rapamycin analogue, and corticosteroids.[110] In this group of 7 animals, host survival was between 9 and 71 days, with a median of 33 days. Acute vascular rejection or cellular rejection caused death in 5 recipients, with 3 developing lymphoproliferative disease. The incidence of lymphoproliferative disease (in 3 of 7 recipients), on some occasions developing coincidentally with histopathologic features of rejection in the transplanted kidney, suggests that the immunosuppressive regimen was excessive and yet failed to prevent the recipients' anti-porcine immune response. Adding soluble complement receptor I to the therapeutic regimen may further extend median survival.[112] A review of the results of pig-to-primate organ transplantation carried out to date would suggest that the immunosuppressive regimens used may not be truly clinically applicable, as a high incidence of drug-induced complications have occurred.

Some involved in the experimental study of XTx believe that unless new, more potent immunosuppressive agents are introduced and these are associated with few complications and side effects, only the induction of immunologic tolerance in the recipient to the pig organ will allow truly long-term survival of pig organs transplanted into humans.[113–115] Researchers are intensively investigating this approach.[116] Although T-cell tolerance to a renal allograft has been achieved in non-human

primates,[117] and both B- and T-cell tolerance have been demonstrated in a murine allograft model,[118] this approach has not yet proved successful in the discordant pig-to-baboon model.[33,48,101]

Likely a combination of approaches both to modify the donor organ (the use of genetic engineering with or without nuclear transfer technology to reduce the expression of the important Gal epitopes or to provide protection from human complement) and to manipulate the immune system of the recipient (antibody or complement depletion/inhibition, T- and B-cell suppression/tolerance) will be necessary to achieve truly long-term function of pig hearts and lungs in humans.

6.4 Risk of Infection

Considerable attention has been paid to the risk of transferring a porcine infection with the transplanted organ to the human recipient and, furthermore, to the risk of the recipient transferring this novel infection to other members of the community.[119–124] Infections transferred with a xenotransplanted organ are termed "xenozoonoses" or "xenoses." Expert opinion, however, holds that if the organ-source pigs are bred and maintained under specific conditions that minimize the risk of infection to the pig, the risk of transferring *known* porcine infections to the human subject will be small, if not minimal.[125] Introducing new viruses, such as the Nipah virus that caused the deaths of more than 100 pig handlers in Southeast Asia in 1999 and necessitated slaughter of more than 1 million pigs,[126,127] should be prevented by the conditions in which pigs will be bred and housed.[125] Indeed, pigs bred and housed under these conditions should provide less risk of infection than the average brain-dead human organ donor, who frequently carries viruses (e.g., cytomegalovirus and Epstein-Barr viruses, or in some cases, more serious viruses, e.g. the hepatitis or human immunodeficiency viruses) that are transferred to the organ recipient.[128–130]

Porcine endogenous retroviruses (PERVs), however, that probably make up approximately 1% of the genome of pig cells, will inevitably be transferred with the organ into the recipient.[121,125,131–134] Studies have demonstrated that the in vitro co-culture of porcine cells with human cells can result in transfer of PERVs into human cells.[131,133,135–137] To date, no evidence suggests that this occurs in vivo.[138–140] However, as truly long-term survival of a porcine organ in a human or non-human primate has not yet been achieved, this possibility remains unanswered. Even if transfer of 1 or more PERVs occurs, however, it remains uncertain whether this will be detrimental to the human host. Of greater concern is the potential risk that a PERV could be transferred from the organ recipient to other members of the community.

Furthermore, recombination of porcine retroviral elements may take place with human retroviral elements, leading to the formation of a new endogenous retrovirus that could have potential detrimental effects. Such a new virus could possibly result in malignant change in the cell or in the development of an immunodeficient state. If this took many years to develop, the patient may well have benefited greatly from the xenotransplant. Nevertheless, any new endogenous retroviral infection could be passed to other members of the community or could potentially infect commercial pig herds.

In view of the latent period of many retroviruses, many years may pass after an initial clinical trial of XTx before the safety or lack of safety to the patient or to the community can be determined. Some encouraging preliminary data from Patience et al,[141] however, lend hope that PERVs may not be the potentially major problem anticipated to date. This group has identified a genotype of pig from which the PERV in the cells cannot be transferred to human cells. To date, it has not been possible to infect human cells with PERV co-cultured from these pig cells under any conditions.

However, this area needs further study and resolution before clinical XTx should be considered safe for the community.

6.5 Porcine Organ Function in the Human Host

Biochemical data that illustrate the degree of metabolic incompatibility between the pig and the human indicate the phylogenetic distance between the 2 species (Table V). Albumin is made up of a sequence of amino acids known to change at a similar rate in different species over a given period of evolutionary time. The more recent the common ancestor that the 2 species share, the closer the amino acid sequence. The evolutionary difference between humans (with an arbitrary score of 1) and pigs (with a relative score of >35) is markedly greater than that between humans and the higher non-human primates (with relative scores of <3), and indicates the metabolic disparity between pigs and humans.

Hammer has reviewed in detail the functional and biochemical discrepancies between humans and pigs.[142,143] He has drawn attention to numerous factors

TABLE V Comparison of the evolutionary relationship between certain primate and non-primate species[a]

Species	Index of dissimilarity[a]
Primates	
Humans and apes	
Human	1.0
Chimpanzee	1.14
Gorilla	1.09
Orangutan	1.22
Gibbon	1.28–1.30
Old World monkeys	2.23–2.65
New World monkeys	2.7–5.0
Prosimians, e.g., lemur	8.6–18
Non-primates	
Bull	23
Pig	>35

[a]Adapted from the work of V. M. Sarich. In: *Perspectives on Human Evolution*, Washburn SL and Jay PC, eds. New York: Hold, Rhinehart and Winston, 1968.

that may modify or impair the function of a pig organ if transplanted into a human. These are too numerous to detail here, but certain aspects of potential physiologic incompatibilities are worthy of comment:

1. The human posture is upright, and the blood supply to the lungs in upright animals is significantly different from that of the lungs in horizontal animals, such as the pig. Similarly, the pig heart functions in a horizontal animal. Will it function equally well in the upright human?
2. The pig's normal body temperature is approximately 102.5°F (39°C), 3 to 4°F or so above that of a human (98.6°F, 37°C). The difference in temperature, and in certain other parameters, such as pH, may affect metabolic activities in the transplanted organ. Although many of these relate to the function of the liver, rather than to that of the heart or lungs, some may be important to the success of the XTx of a thoracic organ.
3. The serum cholesterol in the pig is approximately 45 mg/100 ml, significantly less than that in the human (120 to 200 mg/100 ml). Although this difference may partly be due to differences in diet, it is conceivable that a pig heart transplanted into the human-body environment may be more susceptible to atherosclerotic change than when in its natural environment.
4. It remains uncertain whether human growth hormone will influence the growth of a transplanted pig organ, or whether the organ will have an inherent growth pattern that may be incompatible with that of the human recipient. As a result, in a child, the transplanted pig thoracic organ may not grow sufficiently to keep up with the demands of the maturing human body. Alternatively, it could grow inordinately fast, and its function may become compromised by inadequate growth of the thoracic cavity. Problems with regard to rate of growth may be overcome partly by using miniature swine, which grow to a maximum size of <300 lb (135 kg), in contrast to normal swine that may grow up to 1,000 lb (450 kg). Furthermore, the ready availability of new pig organs would enable retransplantation if size discrepancy between organ and recipient became a problem. Nevertheless, this subject requires further data before cardiac or pulmonary XTx should be offered to infants and children.
5. Pigs have been used extensively in research relating to heart function,[144] although relatively few data exist with regard to lung function. The hemodynamic performance of the pig heart is similar to that of the human heart (Table VI). However, the pig's right ventricle responds less well to volume loading than the human's right ventricle,[145] which could prove problematic in the early post-transplant period.

6.6 Ethical Considerations

The ethical aspects of XTx are numerous, and several individuals and groups have considered them.[13,21,146–152] The potential benefits of XTx (if successful) to the patient,[21] however, are sometimes overlooked in this discussion. The ready availability of pig organs would obviate the frequently long (and often expensive) delay that occurs between determining that the patient is a candidate for a transplant and performing the transplant procedure. Pretransplant morbidity (and mortality) would potentially be reduced and, as a result of the improved physical status of the patient at transplant, post-transplant outcome should improve. The operative procedure could be performed electively rather than under emergency conditions, another factor that should result in improved outcome. Ethical objections to XTx must therefore be weighed against these potential benefits for patients dying of end-stage cardiac or pulmonary disease.

Although limited data exist on which to base a conclusion, if XTx proves successful, the use of pigs as donors will likely be culturally acceptable to many in both the West and the developing worlds. In most

TABLE VI Normal hemodynamic parameters in humans and pigs*

	Human[a]	Pig[e,f]
Heart rate (bpm)	60–100	95–115
Stroke index[b]	32–58 ml/m^2[c]	0.43–1.92 ml/kg[b,g]
Ejection fraction	0.59–0.75[c]	0.40–0.44[h]
Cardiac output (l/min)	4–6[d]	8–10[g]
Cardiac output index[b]	2.6–4.2 l/min/m^2	45–240 ml/min/kg[b,g]
Blood pressures (mm Hg)		
Right atrium	0–8	2–10
Right ventricle	15–30/0–8	22–31/1–6
Pulmonary artery	15–30/3–12	14–22
Left atrium and PCWP	1–10	10–14
Left ventricle	100–140/3–12	56–120/2–8
Mean arterial pressure	70–105	45–89
Systemic vascular resistance (dynes · sec · cm^{-5})	700–1600	2540–2850[i]
Pulmonary vascular resistance (dynes · sec · cm^{-5})	20–130	350–420[i]

*Source: Appel JZ, Buhler L, Cooper DKC. The pig as a source of cardiac xenografts. *J Cardiac Surg* (In press).
[a]Unless otherwise indicated, human data from Grossman W, Barry WH. Cardiac catheterization. In: Braunwald E, ed. *Heart Disease*. Philadelphia, W.B. Saunders: 1998, p. 242.
[b]Estimation of body surface area has proved difficult in pigs, necessitating the use of inconsistent units for these measurements.
[c]Data from Little WC, Braunwald E. Assessment of cardiac function. In: Braunwald E, ed. *Heart Disease*. Philadelphia, W.B. Saunders; 1998, p. 421.
[d]Data from Anderson RW, Vaslef SN. Shock—causes and management of circulatory collapse. In: Sabiston DC, ed. *Textbook of Surgery*, 15th edition. Philadelphia: W.B. Saunders, 1997, p. 68.
[e]Unless otherwise indicated, swine data from Smith AC, Spinale, FG, Swindle MM. Cardiac function and morphology of Hanford miniature swine and Yucatan miniature and microswine. *Lab Anim Sci* 1990;40:47–50.
[f]Cardiovascular parameters in swine vary with weight and breed. Range of some data is wide as they were selected from studies using pigs of appropriate weight but of several different breeds.
[g]Data from Hannon JP. Hemodynamic characteristics of the conscious resting pig: a brief review. In: Tumbleson ME, ed. *Swine in Biomedical Research*. New York: Plenum, 1986, p. 1341.
[h]Data from Gepstein L, Hayam G, Shpun S, Ben-Haim SA. Hemodynamic evaluation of the heart with a nonfluoroscopic electromechanical mapping technique. *Circulation*. 1996;96:3672.
[i]Data from Hughes HC. Swine in cardiovascular research. *Lab Anim Sci* 1986;36:348–350.
PCWP, pulmonary capillary wedge pressure.

cultures or societies, few objections have been raised to transplantation of pig tissues, such as porcine cardiac valves, or to the use of porcine-derived insulin. However, greater reservations may arise to the transplantation of whole porcine organs. The general principles of regarding life as sacred and for society to do all in its power to preserve life (a philosophy shared by several religions, including Islam and Judaism) overcome potential ethical concerns in this respect. However, several ethnic or religious groups are likely to have cultural or religious objections to the use of organs from pigs, even when offered as life-saving measures. Buddhism, for example, may not allow XTx on the grounds that humans have a responsibility to protect other animal species.

Some religious and secular authors, as well as environmentalists, oppose xenotransplantation because they regard it as interfering with the laws of nature. Viewing animal species as either evolving or being created as distinct and apart from one another, these authors view xenotransplants as an immoral, distasteful, and impermissible bridging of natural boundaries.[153] Opponents of this view point out that attempts to implant animal organs and tissues into humans for medical purposes have occurred for centuries,[21] as have efforts by agriculturists, scientists, engineers, doctors, and others to manipulate nature toward human ends.[154]

Several authors have discussed the ethics of using pig organs for XTx. Because pigs are slaughtered in large numbers for human food (approximately 100 million annually in the United States alone)[155] and have been the source of heart valves for several thousand patients in recent years, it does not seem significantly different to use them to supply hearts and lungs. Concern has been raised, however, about genetic modification of pigs through introduction of human genes, and this is clearly unacceptable to some members of the community. Others have indicated that such modification of the pig is acceptable as long as it is not carried to the extent that the pig loses the characteristics of being a pig.[13] The development of

hybrid animals with both pig and human characteristics would be unacceptable.

Concerns regarding housing and care of organ-source pigs have been raised. These relate more to animal welfare than to animal rights. Every effort should be made to ensure that the quality of life of organ-source pigs is as good as can be achieved under the circumstances of their maintenance. Although these pigs will be housed indoors, necessarily isolated from other animals to protect against transfer of animal- or insect-borne infection, they will be housed in cohorts (rather than individually), allowing social contact. Veterinarians will carefully maintain and monitor them to a much greater extent than they do most domesticated or farm animals. The Advisory Group on the Ethics of Xenotransplantation in the UK concluded that the acceptability of using pigs lies in balancing the benefit to humans against the potential harm to the pig or to the human community.[13]

Ethical concerns have also been raised as to whether so many intellectual and financial resources should be concentrated on developing XTx. The governments of most developing countries will almost certainly conclude that such resources should not be concentrated toward the care of relatively few patients when so many more pressing health problems need consideration. But even in the developed world, society must address this question. Although this topic is beyond the remit of this committee, the community surely has a duty to allocate its resources to include support of minorities with special problems.

Additional ethical concerns are inherent to the discussions that follow. These include establishing what conditions should be met before clinical trials begin (see Sections 7.0 and 12.0); harm/benefit assessments with respect to the onset of clinical trials (Section 7.1); the selection of patients for these trials (Section 8.0), including whether and when children should be considered as subjects (Section 8.4); and determining when clinical trials should be expanded (Section 9.0). In addition, ethical issues are raised with respect to complexities of informed consent for trial subjects[150,151] and the possible psychological consequences of living with animal organs.[147]

7.0 EXPERIMENTAL RESULTS NECESSARY FOR CLINICAL TRIAL

7.1 Heart

More than a decade ago, the Columbia group in New York demonstrated in a concordant cardiac xenograft model that prolonged survival in the heterotopic (non-life-supporting) position is not necessarily reproduced in the orthotopic (life-supporting) position.[156] Results obtained by heterotopic HTx in the pig-to–non-human primate model are similarly significantly longer than those reported after orthotopic HTx.[65,76,83,109] Results of non–life-supporting heterotopic HTx in animal models are therefore not sufficient for progression to a clinical trial and need to be validated by orthotopic HTx before clinical trial can be undertaken.

If the pig heart were to be transplanted as a permanent implant (with no plan to replace it with an allograft when a human heart became available), this would be carried out in patients for whom no other form of medical or surgical therapy was deemed suitable (as we discuss in Section 8.2). Because XTx is in its infancy and will undoubtedly advance from experience gained from a clinical trial, the demands placed on those working with experimental animal models should not be excessive. We believe that it should be demonstrable that survival will be obtained comparable to that of patients who received orthotopic heart transplants at the leading centers in the pre-cyclosporine era. The few centers offering this form of therapy in the 1970s obtained 1-year survival of 50% with difficulty. Even with today's more rigorous public scrutiny of medical innovations and the changed medico-legal environment,[157] considering a clinical trial of permanent heart replacement is reasonable if these survival rates can be anticipated. Failure of a premature clinical trial to attain comparable results (as was the case with the results at most of the early HTx centers) might have a detrimental effect on the future development of XTx and on allotransplantation in general. However, because permanent cardiac xenografts would initially be offered to patients not eligible for allotransplantation and for whom no other treatment option is available, a relatively low success rate would seem acceptable for beginning a trial.

In considering what survival target that those in this experimental field should meet before initiating a clinical trial, we reviewed the literature, which indicated that few transplantation studies in non-human primates have been followed for long periods (>6 months). This in part reflects the difficulties of managing these experimental animals when immunosuppressive agents have to be administered on a daily basis. We considered a 3-month period of a life-supporting organ graft in the absence of complications of excessive immunosuppressive therapy as a sufficient minimum for perhaps initiating a clinical trial. Survival of some animals for >6 months would be particularly encouraging (and es-

sential if the organ xenograft were to permanently replace the native organ) as long as the animals remained healthy and were not experiencing serious drug-related complications. Most (but not all of us) thought that to require survival of >1 year is too demanding. Nevertheless, survival of animals for such a period would greatly facilitate a decision to undertake a clinical trial. We would stress, however, that these guidelines should be reviewed at intervals in light of further developments in experimental XTx.

We suggest that the survival rate of animals at 3 months be at least 60% of a series of consecutive life-supporting experiments, with a minimum number of 10 non-human primates surviving for this period of time. For example, if the first 10 non-human primates that receive porcine HTx survived 3 months, this would be sufficient. However, if only 60% survival were achieved, a minimum of 16 transplants would need to be performed to obtain 10 survivors. We are divided as to what target should be set for survival at 6 months. Some of us believe that a minimum survival of 50% of the initial number of animals at 6 months should be demonstrated. Bearing in mind the difficulties of maintaining non-human primates under experimental conditions for prolonged periods, others believe that it would be sufficient to demonstrate only that 6-month survival is possible, e.g., perhaps following only 1 or 2 of the 10 3-month survivors to 6 months to reach this goal. (In general, those members of the committee with personal experience of the difficulties in managing non-human primates under experimental conditions favored the less rigorous goal.) These goals should be attained in a pig-to–non-human primate model, and evidence should be provided that the immunosuppressive regimen is well-tolerated and not excessive (e.g., is not associated with major or repeated infectious complications, significant weight loss, or early development of lymphoproliferative disease). We accept, however, that the period of follow-up envisioned (6 months) is not adequate to ensure that any or all of these complications may not occur subsequently.

All non-human primates in this study should have been treated with the same protocol or with minor modifications. This protocol would form the basis of the prospective clinical trial. Researchers should also provide evidence that hyperacute rejection, acute vascular rejection, and acute cellular rejection can be prevented or reversed. Details of monitoring for rejection, diagnosing rejection, and treating rejection should be provided. Evidence should be provided that the recipients remained healthy at the 3- and 6-month observation points without major complications from the therapeutic regimen. In other words, evidence for good "functional" survival should be provided.

The difficulties of managing non-human primates, particularly if immunosuppressed, are considerable. It is undoubtedly easier to manage a human patient undergoing the same procedures and therapy in the clinical setting, where conditions for maintaining the patient are greatly superior to those of the experimental laboratory. In particular, the ability to diagnose and treat rejection and infection episodes is greatly enhanced in the hospital setting. For these reasons, we have suggested targets that some may believe are relatively lenient, enabling a clinical trial to be considered with little or no evidence of truly long-term (e.g., >1 year) survival of the experimental animal undergoing XTx. However, given the difficulties of managing non-human primates after life-supporting organ transplantation, to set the target too high may delay a clinical trial that could prove lifesaving to a small number of patients.

Given the considerable limitations of the experimental laboratory, it is nevertheless possible to maintain non-human primates with functioning allografts and concordant xenografts for the periods of time we suggest.[117,158–164] A few studies in the literature report of monkeys surviving with life-supporting renal, cardiac, or heart–lung allografts for >3 months,[117,158,161–164] of baboons surviving with life-supporting concordant cardiac xenografts for >3 months[160,165–167] or with non–life-supporting concordant cardiac xenografts for >1 year,[159,168] and of monkeys surviving with concordant kidney or liver xenografts for >3 months.[169]

If the therapeutic regimen is efficient and immune manipulation does not have to be excessive to control rejection, we believe it should be possible to meet the survival targets that we have outlined above. Failure to attain these goals to date illustrates that the currently tested therapeutic regimens are inadequate or that immune manipulation is excessive.

As we discuss in Section 8.2., we believe that few indications exist for an initial clinical trial in which a pig heart is used as a bridging device to a subsequent allograft, and we do not advocate this approach. However, if XTx were to act as a bridge, then we suggest the same 3-month survival of an orthotopic HTx in a non-human primate as outlined above (namely 60% survival at 3 months with a minimum of 10 animals surviving for this period). Implanta-

tion of a mechanical ventricular assist device as a bridge to a human heart transplant results in about 60% to 70% of patients eventually surviving to transplant,[170–173] usually performed within 90 days after assist-device implantation and frequently earlier. It would therefore seem reasonable to require a similar survival if a xenotransplant were used as a bridge. The result would need to be achieved with an acceptable immunosuppressive protocol that would be feasible in patients. (We discuss details of such a clinical trial in Sections 8.1 and 8.2.)

Some might argue that as some patients receive an allotransplant within 30 days of implantation of a mechanical assist device, then 30 day-survival of an experimental xenograft might be sufficient. However, some patients have not stabilized their renal and hepatic function within 30 days. With absolutely no previous experience of xenografts on which to base recommendations, we think evidence that the xenograft will function adequately without excessive immunosuppressive therapy for longer than the minimum period of time required to obtain an allograft for the patient is necessary. The outcome of allotransplantation is likely to be very poor if, by the time the patient undergoes this procedure, he or she already suffers the complications of excessive immunosuppressive therapy.

A bridging trial necessitates the sequential transplantation of an allograft after a period of support with a xenograft. For this approach to be successful, we must confirm that the development of an immune response to transplanted porcine tissues will not be detrimental to the success of the subsequent allotransplant. Few experimental data indicate the outcome of allotransplantation after either concordant or discordant XTx,[174–176] but those few studies that have been reported suggest that prior discordant XTx is not detrimental to subsequent allotransplantation.[174] However, before drawing a definite conclusion, we must confirm these data by sequential pig-to-baboon HTx followed immediately by allotransplantation. We therefore recommend that the results of such studies must be available before a clinical bridging trial is undertaken.

7.2 Lung

In view of the extremely primitive state of experimental lung XTx at present, it may be premature to offer definitive guidance on initiating a clinical trial. However, as with cardiac XTx, 2 different lung XTx clinical trials could be envisioned. A pig lung could be used as a bridging therapy for a patient who urgently requires treatment for lung failure and who would receive an allograft as soon as it became available. Alternatively, a lung xenograft could be employed as definitive therapy for end-stage lung disease without the intention of later allotransplantation.

We recommend the same survival rates in this experimental model as for cardiac XTx. For a permanent trial, a 60% 3-month xenograft survival rate with a minimum of 10 surviving animals at this time should be achieved in a life-supporting pig-to–non-human primate pulmonary XTx model, with evidence of control of rejection using an immunosuppressive regimen that is feasible for human patients. We are again divided on whether a 50% 6-month survival is also required or only evidence that 6-month survival is possible. A trial of bridging lung XTx would require a 60% 3-month survival following transplantation of a life-supporting lung in a non-human primate.

Given the intensive immunosuppressive therapy that may be required to achieve even short-term xenograft survival, the view that xenotolerance probably has to be induced to achieve acceptable long-term survival rates is persuasive. If this proves to be the case, then this must be demonstrated in the relevant pig-to–non-human primate model before clinical XTx can be employed as a permanent treatment modality.

8.0. PATIENT SELECTION FOR INITIAL CLINICAL TRIAL

8.1 General Considerations

No clinical trial should be initiated until expert opinion and the regulatory authorities believe that the risk to the public health is minimal, that pig heart function in non-human primates has been satisfactorily demonstrated (and therefore likely to be satisfactory in the human host), and that the goals set out in Section 7.0 have been fully achieved. If the trial were to include children, additional experimental data regarding the relative growth rates of the transplanted pig organ and the immature host would be required. We should restrict clinical XTx to recognized centers of excellence that have experience in the relevant clinical allotransplantation *and* experimental XTx. Patients who are moribund or so terminally ill that they would not benefit from the procedure should be excluded. We accept, however, that we cannot ascertain the potential risks of XTx with certainty by any approach other than a clinical trial.

Currently, a number of cell and tissue XTx trials are occurring in human patients (Table VII), and the data from these are steadily becoming available. Information from these trials may provide data on

TABLE VII Current or recent clinical trials of xenotransplantation or exposure to xeno tissues in the United States and Europe

Patient's disease	Tissues/cells transplanted	Donor species
Liver failure	Hepatocytes[a] Whole liver[a]	Pig
Diabetes mellitus	Pancreatic islets	Pig
Degenerative neurologic diseases	Neuronal cells Engineered kidney cells	Pig Hamster
AIDS (HIV I)	Bone marrow cells	Baboon
Refractory pain (terminal cancer)	Adrenal (chromaffin) cells	Cow

Source: Cooper DKC, Lanza RP.[21]
[a]Patient's blood perfused (1) ex vivo through an artificial liver (consisting of isolated pig cells) or (2) through a whole pig liver (which is not actually transplanted into the patient's body).

the potential risk of xenozoonoses. Similarly, data gleaned from ex vivo porcine liver perfusion in treating patients with fulminant hepatic failure are also becoming available.[177] Furthermore, some could make a case for using the kidney for initial clinical trial of XTx, because patients might receive support by dialysis in the event of graft failure. However, a clinical trial of organ XTx will put the patient at risk for potential complications both of the transplant, e.g., disseminated intravascular coagulation, and of immunosuppressive therapy. The fact that an effective form of long-term therapy, namely dialysis, is available to patients with end-stage renal disease, therefore, has to be weighed against the potential benefits and risks of an experimental procedure, such as XTx. We believe, however, that patients with end-stage cardiac or pulmonary disease may represent ideal candidates when no other therapy will support life. Although we do not believe it is essential to have results from trials of cell or renal XTx before initiating a trial of porcine thoracic organ transplantation in humans, all of the data accumulated from previous trials should be carefully considered before embarking on clinical heart or lung XTx.

Some have suggested that patients highly sensitized to HLA antigens might be ideal candidates for the initial XTx clinical trial because it may be difficult, or impossible, to obtain suitable human organs for them. However, conflicting data exist with regard to whether cross-reactivity occurs between HLA antibodies and anti-pig antibodies, which might lead to early graft failure from a humoral response or at least complicate post-operative patient management.[178–181] Furthermore, even fewer data exist on whether T-cell sensitization (rather than B-cell sensitization) might also lead to failure of the porcine graft because of accelerated acute cellular rejection.[182] We need further information on both these aspects before it would be justified to undertake clinical XTx in a highly sensitized patient.

Cases can be made for the initial clinical trial to be either for permanent replacement of the diseased organ or as a bridge to allotransplantation. Our preference is for the initial trial to be for permanent replacement, but we do not entirely rule out a bridging trial. Although a bridging trial would not begin to alleviate the shortage of donor organs, and would in fact temporarily and minimally increase the demand for allografts as these patients await human donor organs, under certain conditions this would be an ethical way to initiate a clinical trial of XTx. We would stress, however, that bridging should be carried out only in a strictly limited number of patients (e.g., 10 to 20) to allow assessment of whether a thoracic-organ xenotransplant can be maintained successfully for a period of weeks or months. The trial would give valuable information on whether rejection of the transplanted pig organ will occur in a human patient undergoing a protocol found successful in non-human primates, and whether rejection can be reversed with the immunosuppressive drugs currently available. (The experience gained would enable a conclusion on the likely success of XTx as a permanent form of therapy. If the conclusion for the bridging trial were that XTx is not at the stage of development necessary for permanent therapy, then no further bridging trials should be performed until laboratory work indicated that the outcome of a new clinical trial is likely to improve.)

8.2 Heart

8.2.1 Permanent Implantation of a Pig Heart

A case could be made for proceeding to a definitive trial by including patients who are in end-stage failure but *who are unacceptable for allotransplantation*. It may be difficult to identify these patients who have end-stage organ failure but who, despite standard oral cardiac failure therapy, have remained in heart failure (New York Heart Association Class IV) >60 days and who have an estimated 30% to 60% mortality within a few weeks. These would likely be patients with low exercise oxygen consumption (VO_2 <10 ml/kg/min or <50% predicted) and

low ejection fraction. Dependence on chronic intravenous inotropic agents or on intra-aortic balloon pump support would be an added indication.

These patients, for example, would have concomitant disease of other organs (e.g., diabetes, peripheral vascular disease, hepatitis B or C) or would be an older age group, comparable to those currently considered for permanent implantation of a mechanical assist device. Selection of such patients must be careful, as selection of patients with factors that prohibit allotransplantation might reduce the possibility of success. Patients who possibly should be excluded might include those on ventilator support, with active neoplasia, failure of other organs, high irreversible pulmonary resistance, uncontrolled sepsis, and those incapable of understanding informed consent or of collaborating in the trial. Failure of such a trial might set back progress in XTx for a considerable time, and public reaction to transplantation in general might be adverse. The result of the trial would at least provide comparative data between the outcome of short- or medium-term XTx with those of permanent mechanical assist support and of allotransplantation.

The question has been raised as to whether any patient should be considered for a permanent cardiac xenograft when researchers at several centers are currently exploring permanent mechanical assist device support. The number of mechanical assist devices implanted as permanent support, however, remains relatively few, and the long-term results are not yet clear. We conclude that chronic assist device support has not yet been conclusively proven beneficial. Furthermore, at several experienced cardiac transplant centers (generally outside of the United States), mechanical assist devices are not readily available. We believe, therefore, that given these circumstances and acceptable experimental results of XTx, it would be ethical to perform a clinical trial of cardiac XTx as a definitive therapeutic procedure.

8.2.2 Bridging with a Pig Heart

Mechanical assist device support is currently the preferred form of bridging a patient to allograft, and should be carried out whenever a suitable assist device is available. Patient selection for a bridging-by-XTx trial may be difficult because relatively few patients would not be suitable for bridging with a mechanical assist device. The ethics of bridging with a xenograft if the patient is suitable for bridging with a mechanical assist device, if one is available, are questionable. However, in some cardiac transplant centers, mechanical assist devices are not available, and patients exist in whom these devices cannot be implanted. We believe that only patients unsuitable for assist device support should be selected for the initial clinical trial. In particular, we believe that some patients who require biventricular support could be candidates for bridging by XTx, although it may be difficult to identify these patients before left ventricular support has been provided. However, other patients could be included if assist device support were unavailable when indicated.

We believe that bridging is best justified if it would not only maintain the patient until an allograft became available, but would also improve the patient's condition and make him or her more likely to survive the allotransplant procedure. The experimental results that had been obtained would largely predict the likelihood that a xenograft would improve the patient's condition. If these results suggested that XTx would maintain the patient's hemodynamic status only at the expense of general deterioration or would be associated with a major increase in risk from excessive immunosuppressive therapy (as is the case with the majority of preclinical experimental trials reported to date), then the bridging trial should not occur. Indications for XTx bridging would therefore be similar to those for mechanical assist device bridging, in which improvement of the patient's condition is also a major goal.

Patients to be bridged should in every way be suitable candidates for clinical orthotopic allotransplantation. The standard criteria for selection of heart transplant recipients for allotransplantation should apply. These patients should be rapidly deteriorating with an expected survival of less than 1 to 2 weeks without some form of mechanical assistance or transplantation. However, the transplant should occur before irreversible deterioration of other organs ensues that might militate against successful bridging.

We see multiple ethical concerns if clinicians use XTx bridging as an emergency treatment, e.g., in a patient who cannot be weaned from cardiopulmonary bypass following routine open heart surgery. A major concern is that the patient is unlikely to have given fully informed consent for XTx. If the possibility of XTx had not been fully discussed with the patient before open heart surgery, e.g., a revascularization procedure, or before he or she suffered myocardial infarction, then informed consent must be obtained from the legal relative or representative. Surgeons may therefore need to obtain informed consent under less than ideal emergency conditions. If the patient does not directly give

informed consent, an increased likelihood of patient non-compliance (or legal repercussions) may exist after XTx. We would conclude that these are generally unacceptable circumstances on which to base an initial clinical trial of XTx.

When the bridged patient has improved and has shown stable renal and hepatic function following pig-organ insertion, he or she should be eligible for allotransplantation *under the same regional guidelines* as any patient with a bridging mechanical assist device. This would ensure that no patient in the trial takes precedence over other patients on the waiting list.

Even if intended as a bridge, the initial clinical trial should not include heterotopic HTx in the thorax,[183,184] unless the surgical group is currently carrying out this operation on a regular basis in a significant number of patients annually. If heterotopic HTx is performed in the first clinical trial using pig hearts, a center might face 2 learning experiences at the same time, namely, relating to XTx and to heterotopic HTx. This would not be wise and would mitigate against good results. Heterotopic HTx is technically more demanding than orthotopic HTx, and very few groups have significant experience in this operation. Fewer than 5% of cardiac allotransplants performed worldwide are heterotopic. Furthermore, the success of the trial might be more difficult to assess following heterotopic HTx.

Under most circumstances, we do not believe it would be ethical to place a cardiac xenograft as a bridge and then, in the event of its failure, replace it with a mechanical assist device also intended as a bridging procedure. If the patient is suitable for implantation of a mechanical assist device, and one is available, then one should be implanted as a primary bridging procedure. However, if the patient is suitable for mechanical device implantation, but a device is not available (for whatever reason), and XTx is performed, and this fails before an allograft is offered, and a device is now available, then it would be ethical to replace the porcine organ with the mechanical device.

8.3 Lung

Because experimental lung XTx is in such a primitive state of development, it is clearly premature to consider a clinical trial in detail. However, we offer our guidelines, which may be greatly modified in the light of further research. (We have not considered the possibility of using a pig lung for ex vivo support in patients with end-stage pulmonary failure who are unlikely to survive until an allograft becomes available. This approach may need to be considered if short-term [weeks] function of a pig lung can be demonstrated in a non-human primate, particularly if improvements in the period of support provided by extracorporeal membrane oxygenation [ECMO] or other mechanical devices do not take place.)

We prefer that the initial trial be in patients with end-stage pulmonary failure who are unacceptable as candidates for allotransplantation. However, in some geographic areas, the shortage of human donor lungs is particularly acute and patients on the waiting list may die before an organ becomes available. We therefore believe lung XTx could also be offered under exceptional circumstances to patients on the waiting list who have an extremely limited life expectancy without LTx and who have no realistic chance of a human cadaveric or living lung transplant in their estimated survival time. Those on ventilators or ECMO support or being considered for ventilator/ECMO support, with poor prognosis for lung recovery, could be considered.

Patients on the LTx waiting list who suffer from idiopathic pulmonary fibrosis or primary pulmonary hypertension (PPH) have the shortest life expectancy. The mortality for those with idiopathic pulmonary fibrosis in the Eurotransplant region is 1.55 times higher than for the reference group of patients with cystic fibrosis. Patients with PPH are extremely demanding in their immediate post-operative course after LTx, because a number of physiological problems occur that do not occur in patients undergoing LTx for other conditions. We therefore suggest initially enrolling patients who suffer from idiopathic pulmonary fibrosis and who are progressively deteriorating without a realistic chance of obtaining allotransplant. Criteria that might indicate deterioration with limited life expectancy in this group include (1) progressive rise in pulmonary artery pressure (mean $>$50 mm Hg), (2) hypercapnia (PCO_2 $>$60 mm Hg), and (3) tachypnea ($>$30/min), despite maximal therapy.

In view of the particularly poor outcome after retransplantation, particularly when necessitated by acute graft failure in the early post-LTx period, we do not recommend considering XTx as a bridge to allograft.

8.4 Infants and Children

The question of whether to include infants and children in the initial clinical trial is controversial. Because XTx and clinical trials in children are controversial topics in the community, some make the case that it would be best to avoid this combi-

nation. (The same view should be taken with regard to adults incapable of giving valid consent.) Although we prefer that the initial clinical trial enroll adults, we do not exclude children as potential subjects. The disproportionately high mortality for infants on the waiting list, particularly those with ductal-dependent physiology who have very limited life expectancy, provides a compelling reason not to exclude these patients from consideration. No alternative may be available for the child with, for example, a univentricular heart for which no allograft becomes available. Some argue that successful XTx, even if providing support for only a relatively short period, may enable time to obtain an allograft. Because the Berlin ventricular assist device can be used in children[185] but is not universally available, bridging with a xenograft may be lifesaving.

Although children cannot give fully informed consent for the trial, this is true of all therapy offered to children. The parent or legal guardian must give informed consent on behalf of the child. Parents of infants considered for transplantation are often extremely motivated and well-informed individuals who face many "unknowns." They understand that their child faces a high risk of not obtaining an organ and are thus frequently anxious to look for new, even experimental, options. The inability of the child to give consent should therefore not absolutely preclude him or her from entering into such a trial if it might be lifesaving.

We must consider the question of the transplanted organ's growth[186] and the possible need for retransplantation in the future, as well as the long period of follow-up (with its potential for complications) necessary for the child if XTx were successful.

Although evidence suggests that neonates lack natural anti-Gal antibodies and do not actively develop such antibodies for several weeks, under experimental conditions they rapidly develop them once exposed to pig tissue.[187,188] During cardiopulmonary bypass, plasma exchange could easily remove passively acquired maternal anti-Gal IgG. The rapidity with which IgM and IgG antibodies to Gal determinants develop in the immunologically unmodified (and untransplanted) infant is not well-defined. Nor is it defined in the newborn organ-transplant recipient subjected to systemic immunosuppression, particularly with the newer agents that might suppress B-cell function. Moreover, the possibility that introduction and persistence of the antigenic stimulus, in combination with certain immunosuppressive agents, may prove a tolerogenic interaction is likely to be higher in the newborn that at any later time in life. The fact that the ready availability of xenografts would enable scheduling the surgical procedure within the first few postnatal days, if beneficial, enhances this possibility.

Although evidence suggests that infants accept ABO-incompatible heart transplant with less immune-related problems than do older children and adults,[189,190] no conclusive evidence shows that the immaturity of the immune system in neonates and infants provides a "window of immunologic opportunity" significantly beneficial to the outcome of XTx in this age group. Nevertheless, evidence may emerge that compels us to consider newborns as the most obvious recipient in early clinical trials of XTx, and we should not close the door on that possibility.

If children are considered as recipients, the medical center should demonstrate adequate experience in pediatric HTx (or LTx) and in experimental XTx.

9.0 INITIAL CLINICAL TRIAL RESULTS NECESSARY FOR FURTHER EXPANSION

Any initial clinical trial of implantation of porcine organs (possibly in 10 initial patients) should not be expanded until all patients have been followed for a sufficient period of time to assess outcome. We suggest a minimum follow-up of at least 3 months, and possibly 6 months. Trial expansion should not occur until all 10 initial patients receive this minimum follow-up. If the trial involves infants or children, a longer follow-up might be required to ascertain the relative growth rates of transplanted organs and recipients. We know that such short follow-up is insufficient to exclude the development of many potential xenozoonoses, e.g., latent viral infections, that might potentially be transferred with the porcine organ. To be absolutely certain that no microorganism has been transferred could take 20 or more years. In view of the very small risk that a latent virus might be present, we believe a prolonged wait before proceeding with what might prove successful therapy for thousands of patients would be impractical and unethical.

9.1 Permanent Implantation of a Pig Organ

The criteria of success for a definitive trial of permanent XTx in patients unlikely to benefit from any other form of therapy would be survival in the first year comparable to the results gained in clinical human HTx in the late 1970s or early 1980s before cyclosporine became available (i.e., at the beginning of the majority of current clinical programs when the mean 1-year survival was approximately 50%). Although the results have gradually and significantly improved since that time, we think it reasonable to

judge the early results of thoracic-organ XTx based on those of historical allotransplantation. We emphasize entering patients into the trial who, without XTx, would be expected to survive days to weeks and who are unacceptable for allotransplantation. We believe that 50% 1-year survival would reasonably indicate success of such a trial.

9.2 Bridging with a Pig Organ

If the first group of xenograft recipients had been bridged to human allotransplant with a survival rate close to that for mechanical assist device bridging procedures and with comparable survival after allotransplantation, an extension to a definitive trial of permanent implantation might be justified, particularly if the trial suggests that further improvements in the results are likely. If good function of the xenotransplant occurs without need for excessive immunosuppression to control rejection, and no indication of xenozoonosis transfer results, the trial could be expanded.

9.3 Conclusions

The criteria for success of either a definitive trial or a bridging trial would therefore be 1-year patient survival rate of >50%. Clinical success of <50% might be sufficient criteria to discontinue the clinical trial until further research has been performed, although this decision would depend on the causes of xenograft failure. Xenograft failure caused by rejection or infection associated with excessive immunosuppression would contraindicate expanding the trial. Nevertheless, despite poor initial results in the early days of HTx and LTx, those few groups who persistently pursued scientific programs made steady progress. Unless clinical trials of XTx prove clearly disastrous, continuing cautious clinical development at carefully selected centers might be justified.

10.0 REGULATION OF CLINICAL XENOTRANSPLANTATION

Various government and non-government organizations have given careful consideration to how clinical XTx should be undertaken (see Section 16.0, Appendix 3).[13,147,191–193] Some of these organizations have drawn up guidelines for planning such trials.[14,191]

The possible impact of XTx on the community supports the view that it requires strict regulation and surveillance. Regulation is necessary to ensure animal welfare and also protection of individual patient rights and the rights of the community. These issues demand regulation on the broadest base possible. Local regulation clearly does not fulfill this demand. We advise national regulation as the minimal form of control, but every effort should be made to establish international coordination to ensure a uniform system of regulation. Early and free exchange of information between the various national bodies would be advantageous.

At a national level, existing regulatory agencies should regulate organ xenografts according to existing rules that govern medical devices or biological products, with testing conducted and approval based on considerations for safety and efficacy. Infectious disease monitoring should be obligatory, managed by national (or international) regulatory authorities. We urge the governments/regulatory agencies of all countries in which clinical XTx is likely to take place to set up regulatory bodies with the power to oversee all aspects of such trials.

Although we do not believe an international body can practically provide this regulatory control, we strongly favor international agencies having an active role in the safe development of clinical XTx. International oversight would ensure that no duplication of effort occurs and that only centers with significant experience and expertise in both clinical HTx or LTx and experimental XTx participate in the early clinical trials. We recommend that centers that have developed experience with the particular immunomodulatory regimen in large-animal experimental models perform, or at least direct, the initial trials. Any center that participates in the trial should include personnel who have direct experience with the experimental model. Protocols for a trial must be reviewed and sanctioned by a national or international committee, which has government-designated powers to prevent or discontinue the trial. We recommend that representatives from all countries contemplating approval of XTx clinical trials meet to agree on common regulatory procedures. All data regarding the trial should be accumulated in a national or international registry and be available for subsequent auditing as required. This includes storage of sera taken from patients and close contacts, both before XTx and at regular intervals after XTx. The authorizing committee should review each trial at regular intervals and give permission before researchers continue the trial. We deem essential a central database to collect and collate data on possible xenozoonoses. This would form the basis on which the authorizing committee would decide the necessary steps should a xenozoonosis occur.

An organization such as the ISHLT could play a

valuable role in the international monitoring and coordination of such clinical trials, for example, by maintaining a register of the results of trials relating to heart or lung XTx, and by ensuring that data are widely shared. Indeed, we anticipate that all groups involved in clinical trials will provide data to the ISHLT Registry. The ISHLT could also participate in their regulation if given the support of government organizations.

11.0 FINANCIAL ASPECTS OF CLINICAL TRIAL

Initially, xenotransplantation will be expensive, making it ill-affordable in developing countries, although no hard data presently support this conclusion. Xenotransplantation will compete with cheaper forms of health care that can be applied to a much larger sector of society. As such, competing health care needs (such as immunization, primary and preventive medical care, the increasing burden of caring for patients with AIDS, and basic secondary and tertiary care) will significantly limit XTx in all developing countries. Xenotransplantation is therefore unlikely to have any significant impact on the health care economics of the developing world because financial resources will constrain its introduction.

In the developed world, in light of the progressively aging population, if successful, XTx could significantly impact health care costs, largely by enabling a greater number of thoracic-organ transplants.[194,195] If the clinical trial demonstrates extremely high costs associated with repeated admissions for post-XTx complications, the procedure may be deemed unjustifiable until further medical advances have been made. Considerable reduction could occur, however, in the financial burden incurred by more conventional forms of therapy for end-stage cardiac and pulmonary disease, which is substantial. For example, the ready availability of a pig organ will negate the high costs of maintaining a transplant candidate in an intensive care unit while he or she awaits a donor organ. Overall, however, we anticipate a substantial increase in health care expenditure.

The source of funding for the initial clinical trials will depend to a certain extent on where the clinical trial takes place. In countries in which the health care system is socialized and government-funded, it may be appropriate for the government to participate in supporting such trials. However, because several pharmaceutical and biotechnology companies will ultimately benefit financially if XTx becomes a clinical reality, we think it appropriate that such companies support or contribute toward funding such trials, just as they support trials of novel pharmacologic agents. Although commercial interests play a major role in funding development of XTx, for its introduction on a wide scale, every effort must be made to reduce the associated costs to make it affordable to as many patients as possible.

In the interests of patient safety, however, researchers from various trials should share openly and in a timely fashion data regarding patient treatment protocols and outcomes. They should share these data with a single, central, objective government-supported review board to assure that the inevitable mistakes are not repeated unnecessarily. We prefer organizing this at an international level.

12.0 ARE WE READY FOR CLINICAL TRIAL?

Clinical trials of porcine cell and tissue XTx are already occurring in the United States and in Europe (Table VII). These trials are associated with little immediate risk to the patient, and we hope to glean valuable information from them, particularly with regard to the risk of xenozoonoses. Trials of ex vivo pig liver perfusion in patients with fulminant liver failure are also ongoing, and again may be a source of valuable data when whole-organ XTx trials begin.

Three main questions must be answered before initiating a clinical trial in XTx. The first is whether evidence indicates that the physiologic function of the transplanted organ will be adequate to meet the needs of the patient. With regard to the heart, increasing evidence shows that an orthotopically transplanted pig organ can satisfactorily support the life of a recipient primate. This evidence is not yet available for the porcine lung. The evidence on growth of a transplanted porcine thoracic organ relative to the growth of the recipient remains incomplete. Incompatible growth may disturb xenograft function. This has particular relevance if infants and children are included in a clinical trial.

The second question is whether an immunosuppressive or immunomodulatory regimen has been developed to successfully prevent rejection of the transplanted organ without placing the patient at unacceptably high risk of side effects. With a median 12-day survival of orthotopically placed pig hearts in non-human primates in a group of only 6 baboons (Table IV), a successful immunosuppressive regimen has not yet been satisfactorily demonstrated. The level of immunosuppressive therapy needed for permanent acceptance of a cardiac xenotransplant has not yet been fully defined in an animal model, but the level that will be required appears high. This may well result

in significant risk of infection and malignant disease. With regard to the lung, as yet no evidence suggests that porcine lung survival can be prolonged beyond a few hours.

The third question is whether an infectious agent will be transmitted from the porcine organ into the human recipient and whether this agent will be detrimental to the recipient. More importantly, the question must be extended to ask whether the infectious agent can be passed on and be detrimental to other members of the community. Although it might be acceptable for a dying patient to risk infection with a porcine microorganism, particularly if that organism does not lead to symptomatic disease for several years, it is not acceptable to subject members of the community to such an infection. Current evidence and opinion suggest that the risk of symptomatic infection from transfer of an organism along with the donor organ is small, and that the risk to the general population is even smaller. Nevertheless, the risk of transferring an infectious agent from a porcine organ that has been functioning in the absence of rejection for a long period of time (e.g., at least several months) in a primate recipient has not yet been fully determined. Although data are accumulating fairly quickly, the answer to this third question remains unanswered. In particular, the risk of covert infection in the longer term is unknown.

In view of the above considerations, we think it is premature to initiate a clinical trial at the present time. We believe a premature XTx clinical trial that results in very poor and widely publicized outcomes would adversely affect further development of this promising field, and might also adversely affect human cadaveric organ donation.

13.0 CONCLUSIONS AND RECOMMENDATIONS

13.1 Conclusions

1. A need exists worldwide for an increased supply of donor thoracic organs.
2. Xenotransplantation offers the possibility of an unlimited supply of organs for heart and lung transplantation. These organs would be available when required, enabling elective transplantation.
3. Many unanswered questions remain relating to the immunologic problems of XTx.
4. The results of experimental non–life-supporting HTx or LTx do not reflect those of life-supporting thoracic-organ transplantation, and they do not form a sufficiently acceptable basis on which to proceed to clinical trial.
5. Evidence is insufficient to conclude that the immune response to a cardiac or pulmonary xenograft used to bridge a patient to an allograft will or will not prove detrimental to the function of the subsequent allograft.
6. Evidence is insufficient to conclude that the presence of B- or T-cell allosensitization (e.g., from previous blood transfusion, pregnancy, or allograft) will or will not prove detrimental to the function of a subsequent xenograft.
7. Unanswered questions remain relating to function and growth of the pig heart and lungs in the human metabolic environment. Although evidence suggests that a pig heart can function satisfactorily in the orthotopic position in a primate, evidence with regard to porcine lung function is inadequate to make a conclusion in this respect.
8. A potential risk exists, hitherto undetermined, of transferring an infectious organism along with the donor pig organ to the recipient, and possibly to other members of the community.
9. Current experimental results indicate that a clinical trial of heart XTx at present is premature.
10. Experimental lung XTx is in an extremely primitive stage of development and clinical trial cannot be considered at the present time.
11. Thoracic-organ XTx, when successful, will almost certainly require increased health care spending.
12. Xenotransplantation of thoracic organs theoretically has immense potential, and research in this area should be encouraged and supported.

13.2 Recommendations

1. Every effort should be made to improve the medical treatment of patients with advanced heart and lung disease to minimize the number who need organ transplantation.
2. Every effort should be made to increase the number of human cadaveric organs that become available.
3. A XTx clinical trial should be undertaken only when experts in microbiology and the relevant regulatory authorities consider as minimal the potential risk of transferring a porcine-related infection from the recipient of a pig thoracic organ to other members of the community. *We base the remaining recommendations on the assumption that this recommendation will be fulfilled*.

4. National bodies with wide-reaching government-backed control over all aspects of the trials, including the power to halt them if deemed necessary, should regulate the initial clinical trial and all subsequent clinical XTx procedures for the foreseeable future.
5. An international body that would coordinate the trial and widely disperse information should monitor all clinical trials. The ISHLT could play a leading role in this respect and maintain a registry of all clinical trial results.
6. A XTx clinical trial should begin only after achieving 60% survival of life-supporting pig-to–non-human primate transplants for a minimum of 3 months in a series of consecutive experiments with a minimum of 10 animals surviving for this period of time. If the xenograft is implanted as a permanent replacement of the native organ, evidence must show that some non-human primates survived at least 6 months. Ideally, a 50% 6-month survival should be achieved, but consideration could be given to a clinical trial even if this goal is not attained if all other aspects of the experimental work were encouraging. These goals should be achieved in the absence of life-threatening complications from the immunosuppressive regimen.
7. A bridging trial should be initiated only when substantial evidence suggests that the immune response to the xenograft will not prove detrimental (through a cross-reactive antibody or cellular response) to the subsequent allograft.
8. The relationship between the presence of anti-HLA antibody and anti-pig antibody and their cross-reactivity must be investigated further. The outcome of pig-organ XTx in recipients previously sensitized to HLA antigens by an allograft, pregnancy, or blood transfusion requires further investigation.
9. The patients initially enrolled in a XTx clinical trial should be unacceptable for allotransplantation but should not have such severe concomitant disease or other factors that would greatly diminish the potential for the trial's success. The results of permanent mechanical assist device support currently remain uncertain, and the availability of this form of experimental therapy does not preclude a clinical trial of permanent cardiac XTx and does not render such a trial unethical.
10. A second group to consider for XTx clinical trial includes patients acceptable for allotransplantation but who are unlikely to survive until a human cadaveric organ becomes available and in whom bridging by a mechanical assist device is not possible or is unavailable. Surgeons should not use a xenograft bridge if a mechanical assist device would fulfill this role and is available when required.
11. Awaiting the results of cell or kidney XTx trials is not necessary before initiating a XTx clinical trial of heart or lung.
12. Although the initial clinical trial should ideally not include infants and children, but only adult patients who can give fully-informed consent, infants and children should not be absolutely precluded from the trial.
13. An initial clinical trial conducted in a small number of patients (e.g., 10) should not be expanded until minimum follow-up has been for an adequate period of time to assess the results. We suggest a minimum of 3 months. We recognize that this period is inadequate to assess the potential for medium- and long-term complications.
14. The initial clinical trials should be carried out as an extension of a planned experimental program, and ideally those who have been involved in the experimental development of the protocol should perform or direct the trial.
15. The status of research into XTx should be reviewed at intervals and the above recommendations revised as necessary.
16. To protect integrity and to assure the ongoing success of clinical trials, the ethical issues surrounding XTx should be further explored. This includes the ethical considerations expressly identified and discussed in this report, as well as shared concerns and differences between nations, cultures, and religious traditions within the broader international community.

14.0 APPENDIX 1: THE NEED FOR MORE ORGANS AND THE POTENTIAL FOR THORACIC-ORGAN TRANSPLANTATION

14.1 Heart

Annually approximately 4,000 patients undergo heart transplantation (HTx), although a slight decline in numbers has occurred since 1995 (Figure 1).[196] In the United States, more than 4,250 patients currently await donor hearts, but only one half of these will undergo transplantation in the current year (Table VIII).[197] In the Eurotransplant region (comprising Austria, Belgium, Germany, and the Netherlands), 1,250 new patients were added to the HTx waiting in 1998, whereas only 759 received

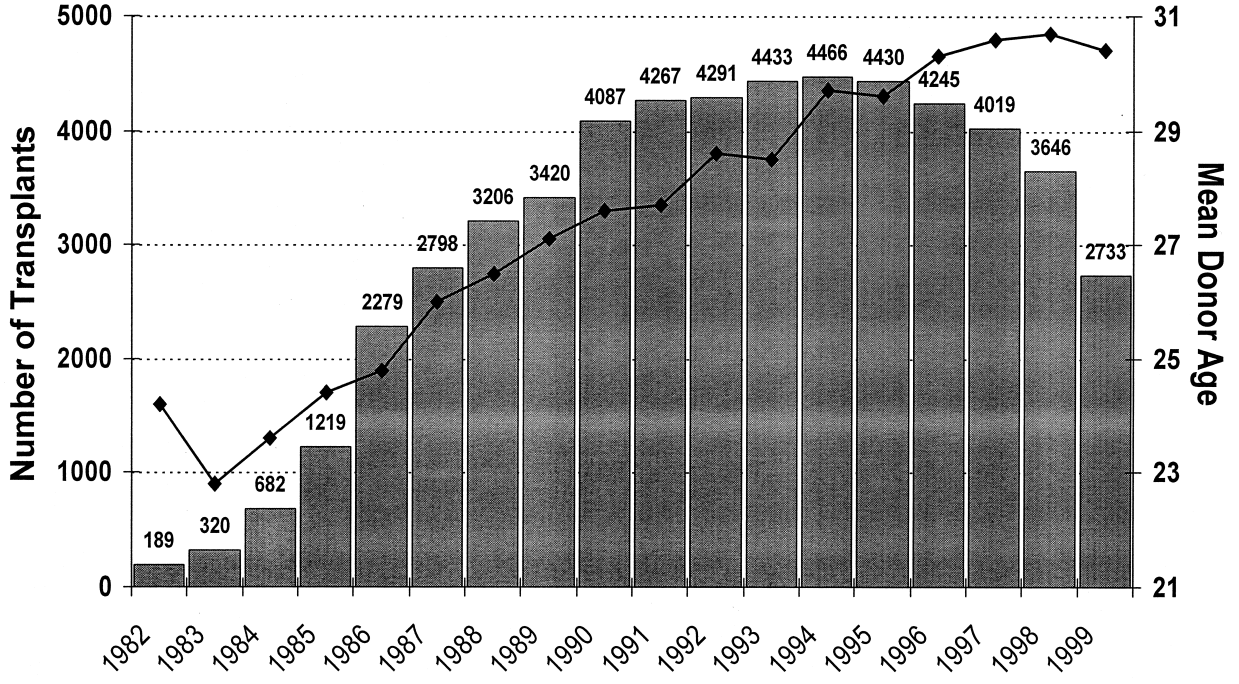

FIGURE 1 Number of heart transplants performed annually worldwide in the years 1982–1999, inclusive (Courtesy J. Hosenpud, MD, International Society for Heart and Lung Transplantation/United Network for Organ Sharing Registry).

transplants during that year (Table IX).[198] For lungs, 341 new registrations were reported in 1998 and 228 lung transplants were performed in that year (Table IX). Table X includes the data for Australia and New Zealand. In most other parts of the world, the number of heart transplants undertaken annually is small compared with the size of the population (Table XI); this is because of a combination of cultural concerns relating to cadaveric organ donation, lack of infrastructure or expertise to manage such patients, and most importantly, lack of financial resources to undertake this type of corrective surgery.

In 1997, the median waiting time for HTx for patients registered in the United States was 207 days (Table XII).[197] In that same year, 774 (10.6%) of the 7,298 patients put on the waiting list for HTx died before receiving donor organs (Table XIII).[197]

Because of cultural factors, the number of cadaveric donor organs that become available in Japan is extremely small (see below). An alterna-

TABLE VIII Number of patients on U.S. waiting lists in 1999[a] and receiving organ transplants in 1997[b]

Organ(s)	Patients on waiting list[a]	Transplants with cadaveric organs[b]	Transplants with living donor organs[b]	Total transplants[b]
Kidney	42,071	7,759	3,669	11,428
Liver	13,095	4,100	68	4,168
Pancreas (or pancreas + kidney)	2,317	1,055	6	1,061
Heart	4,277	2,292	0	2,292
Lung(s)	3,299	911	17	928
Heart + Lungs	238	62	0	62
Intestine	119	65	2	67
TOTAL	63,635	16,244	3,762	20,006

Source: United Network for Organ Sharing (UNOS).
[a]Data as of June 1999.
[b]Data for 1997 from UNOS Annual Report 1998.

TABLE IX Number of patients on the Eurotransplant[a] waiting list and receiving transplants in 1998

Organ(s)	Patients added to waiting list	Cadaveric organs donated	Transplants with living organ donors	Total transplants
Kidney	5,048	3,068	526	3,594
Liver	1,500	1,071	38	1,109
Pancreas (or pancreas + kidney)	356	258	—	258
Heart	1,250	759	—	759
Lung(s)	341	228	—	228
Heart + Lungs	61	20	—	20

Source: Eurotransplant International Foundation Annual Report, 1998.
[a]Eurotransplant comprises Austria, Belgium, Germany, and the Netherlands.

tive source of organs is therefore particularly urgent in Japan.

Clearly difficulty exists in giving an accurate estimate of the number of patients who might benefit from thoracic-organ transplantation if the source of donor organs were unlimited. Evans[199] has attempted to estimate the need and demand for thoracic-organ replacement and the potential supply of donor thoracic organs in the United States (Tables XIV and XV). The considerations discussed below provide some indication of the potential for XTx.

Even if no increase occurs in referral of patients for HTx consideration, a larger number would almost certainly be added to the waiting list if no shortage of donor organs existed. Because many transplant physicians and surgeons hold the view that the valuable donor organ should be used only in patients for whom they anticipate long-term survival, some centers are highly selective in adding patients to the waiting list.

This policy excludes many patients with concomitant disease, such as peripheral vascular disease, diabetes, and sub-optimal function of other organs such as the lungs or kidneys, from being accepted for HTx. Some centers decline to offer transplantation to patients older than aged 65, thus excluding some potentially suitable patients. Similarly, some centers exclude patients for whom they expect psychosocial problems after HTx. Other patients for whom many centers are reluctant to offer HTx include those positive for hepatitis B or hepatitis C and those with amyloid disease, hemochromatosis, thalassemia, and a recent history of malignant disease. If the supply of donor organs were unlimited, many of these patients might receive HTx, even if anticipated survival were only a few years, as long as a transplant could improve their quality of life.

TABLE X Number of patients on Australian and New Zealand thoracic-organ waiting lists on January 7, 2000, and receiving transplants in 1999

Organ(s)	Patients on waiting list	Patients transplanted
Heart	74	76
Lung (single/double)	96	76
Heart + Lungs	8	2

Source: Personal communication from transplant centers to Anne Keogh.

Heart transplantation might be preferable for patients who are poor-risk candidates for myocardial revascularization procedures. Although revascularization procedures are increasingly employed, many patients are left with severe unrevascularizable ischemia.

Approximately 50% of those who undergo HTx at the present time lose graft function within 10 years. Retransplantation is offered to relatively few, largely because of the development of concomitant disease often associated with long-term immunosuppressive therapy. Surgeons would be less reluctant to offer retransplantation if they had a source of readily available donor organs, as these patients would no longer compete with others for this valuable resource.

However, the number of patients currently referred for HTx represents only a small percentage of those in whom transplantation (or some other form of cardiac replacement) could be considered. Estimates of the scope of the population for whom cardiac replacement might be considered depend on the risk involved and the degree of function promised. Data from the United States provide some indication of the potential need for HTx. Heart disease accounts for almost 750,000 deaths per year. Current estimates of 4 to 5 million cases of heart failure in the Unites States must be adjusted to exclude heart failure with relatively preserved ejection fraction. This accounts for heart failure in more than 50% of patients older than aged 65, and is associated with better cardiac output and prognosis than is heart failure with low ejection fraction, although the frequency of rehospitalization is

TABLE XI Number of thoracic-organ transplants performed in selected countries outside of Europe and North America

Hearts	Australia/NZ	Korea	Malaysia	SaudiArabia	Singapore	Taiwan
No. HTx performed	1,099	137	6	78	17	230
Period	1984–97	1992–99	7/96–9/99	1/89–9/99	1990–99	7/87–5/99
No. total months	156	84	38	129	108	142
Population	18.1 m	60 m	22.4 m	20.4 m	3.1 m	21.9 m
HTx/million population/annum	4.67	0.326	0.085	0.356	0.609	1.23

Lungs	Australia/NZ	Saudi Arabia	Taiwan
No. LTx performed	528	7	33
Period	1986–97	1996–97	1991–99
No. total months	132	12	96
Population	18.1 m	20.4 m	21.9 m
LTx/million population/annum	2.65	0.343	0.189

Sources: Numbers of transplants—presentation at 6th CAST meeting, Singapore, September 1999. Population figures from *Asiaweek*, September 24, 1999.
HTx, heart transplantation; LTx, lung transplantation; m, million; NZ, New Zealand.

similar. Many heart failure patients would be excluded from major surgical procedures because of comorbidities, increasingly frequent in patients older than aged 80 and are therefore excluded from the following estimates.

Assuming that most of the 1 million hospitalizations related to heart failure occur in patients with New York Heart Association (NYHA) Class III and IV heart failure, and estimating a 40% annual rate of rehospitalization, density of population and heart failure prevalence by age yields approximately 350,000 patients under aged 80 in the United States with limiting symptoms and low ejection fraction. Advanced heart failure, which has been defined as persistent or recurring symptoms that limit daily life (NYHA Class III and IV) despite use of currently recommended therapies, is estimated at 250,000 patients in the United States. Although the size of this population is expected to diminish with enrollment into programs developed specifically for intensive medical management of advanced heart failure, these data indicate a large pool of patients, a proportion of whom might benefit from heart replacement.

The most thorough trials of aggressive medical therapy suggest that 10% to 30% of patients with advanced heart failure may have truly refractory symptoms,[200,201] for a prevalence of approximately 35,000 to 100,000 in the United States. These numbers, however, have been derived largely from referral populations characterized by younger patients with fewer comorbidities than the typical patient in whom cardiac replacement would be considered if it were not limited

TABLE XII Median waiting time (in days) for an organ transplant for patients registered in the United States in 1997[a]

Kidney	962[b]
Liver	477
Pancreas	281
Pancreas + Kidney	375
Heart	207
Lung(s)	567[c]
Heart + Lungs	740[c]
Intestine	NA

Source: United Network for Organ Sharing Annual Report, 1998.
[a]The last year for which data are available.
[b]Data for 1995. Among patients registered in 1996 and 1997, too few have been transplanted to make it possible to calculate the median waiting times.
[c]Data for 1996.
NA, data not available.

TABLE XIII Number of deaths of patients awaiting an organ transplant in the United States in 1997[a]

Organ(s)	Patients	Deaths	% who died
Kidney	49,762	2,009	4.0
Liver	15,061	1,129	7.5
Pancreas	656	11	1.7
Pancreas + Kidney	2,654	120	4.5
Heart	7,298	774	10.6
Lung(s)	4,056	409	10.1
Heart + Lungs	374	57	15.2
Intestine	NA	NA	NA
TOTAL	79,679	4,327	5.4

Source: United Network for Organ Sharing, December 1998.
[a]The last year for which data are available.
NA, data not available.

TABLE XIV Estimations of the need and demand for thoracic organs for transplantation in the United States

Organ(s)	Need[a]	Demand[b]	Transplants[c]
Heart	48,965	6,962	2,292
Lung(s)	18,450	3,984	911
Heart + lungs	7,750	354	62

Source: Evans RW.[199]
[a]The *need* for organ replacement consists of the sum total of 4 components during an index period (usually 1 year), namely, the numbers of people (1) never listed for organ replacement (e.g., a transplant), (2) awaiting a transplant, (3) who die on the waiting list, and (4) who receive an organ transplant.
[b]The *demand* for organ replacement (e.g., a transplant) consists of those persons who are fully assessed, declared eligible for a transplant, and placed on the waiting list during an index period (usually 1 year). Three relevant components are the numbers of people (1) awaiting a transplant, (2) who die on the waiting list, and (3) who receive an organ transplant.
[c]Based on the year 1997, the most recent year for which relevant data are available.

by donor supply. In general accord with this conclusion, several bodies have estimated that a wearable mechanical assist device might be appropriate for some 35,000 to 75,000 candidates annually.[202,203] Current estimates of the number of patients who might benefit from total artificial hearts (10,000 to 20,000) or left ventricular assist devices (25,000 to 60,000) are similar (O.H. Frazier, personal communication).

An earlier approach derives from the number of deaths annually attributed to causes that HTx could have prevented. This yields 50,000 patients under aged 65, and doubles with every 5-year increase in age distribution. However, the number of these that could be predicted and averted with surgical replacement remains unknown. In this regard, XTx offers the prospect of "instant" HTx for patients who suffer rapid deterioration in cardiac function. For example, the death rate following myocardial infarction in the United States in 1996 was 80.5 per 100,000 people. Estimating a population of 225 million, this equals approximately 180,000 deaths from this cause each year, although some estimates place the number higher. A proportion of these patients, certainly in the thousands, might benefit from HTx if it could be offered instantly. Transplantation might offer some technical advantages over implantation of a mechanical assist device in such cases.

TABLE XV Estimation of the potential donor thoracic organ supply in the United States using 2 different methods, yielding low and high potential estimates, respectively

	Potential numbers	
Organ(s)	Low	High
Heart	5,620	8,884
Lung(s)	10,812	17,286
Heart + lungs	5,406	8,643

Source: Evans RW.[199]

TABLE XVI Estimated number of potential organ donors in Japan

Population with potential to become organ donors aged (15–64 years)[a]	87 million
Annual number of deaths in this age group	200,000
Estimated number with brain death	2000–3000
Estimated number medically suitable as donors	1000–2000
Estimated number willing to donate organs[b]	10–20

[a]The current transplant law requires that donors be no younger than 15 years.
[b]Written consent from the donor during life (e.g., by a living will) is required by law. By current estimation, <1% of the population has given written consent. If 100% of the population provided written consent, the number of suitable donors annually would be 500–1000.

Despite limitations and problems related to transplanting organs from cadaveric donors in North America, Western Europe, and Australasia, patients in these countries have the potential to undergo HTx. For the vast majority of the world's population, however, transplantation of human organs remains virtually impossible. In many countries, removal of organs from brain-dead subjects remains illegal or culturally unacceptable, and as a result, organ transplantation remains minimal. Japan is an excellent example of a country with the advanced surgical technology and expertise to carry out organ transplantation, and yet cadaveric organ transplantation is rarely performed. Only 4 cadaveric heart transplants have been performed in Japan since 1968. Japan's population approaches 50% of that of the United States, and therefore the number of heart transplants anticipated each year could approach 2,000 (Table XVI).

With an unlimited source of organs, the number of transplants performed in other countries, such as South Africa, Korea, Malaysia, Singapore, Taiwan, and possibly India and China, might also

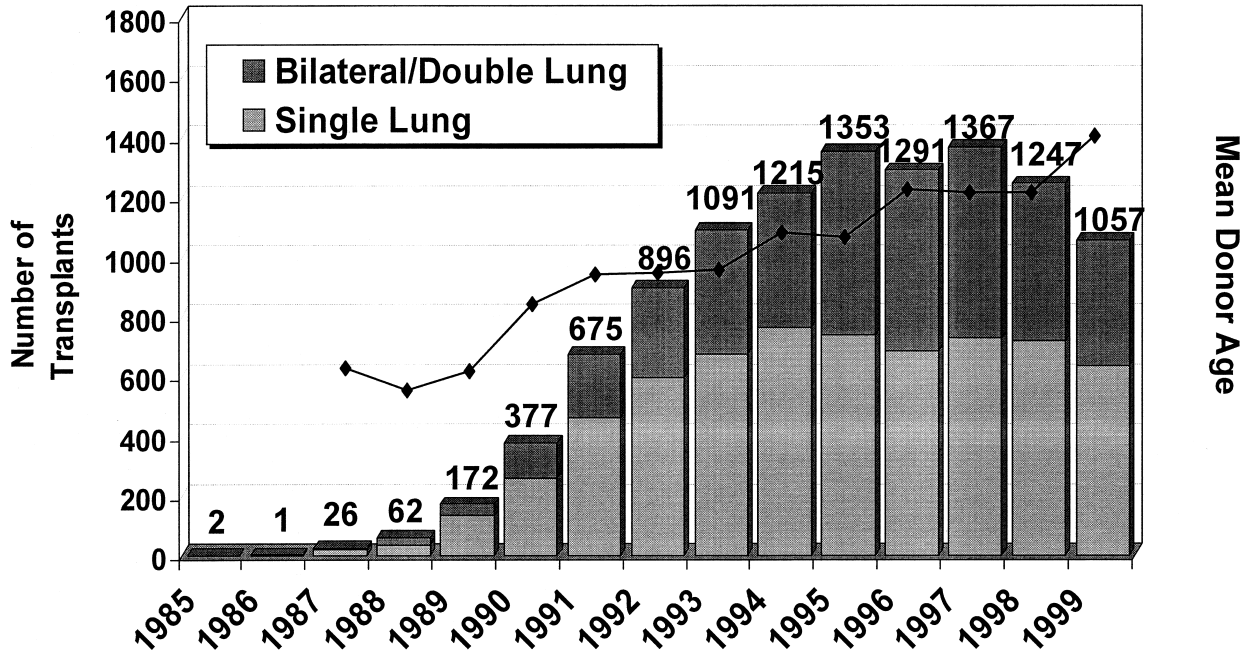

FIGURE 2 Number of single and bilateral/double lung transplants performed annually worldwide in the years 1985–1999, inclusive (Courtesy J. Hosenpud, MD, International Society for Heart and Lung Transplantation/United Network for Organ Sharing Registry).

increase significantly. In many of these countries, financial considerations would limit the number of transplants performed rather than access to donor organs. Nevertheless, HTx could be offered to a number of patients if donor organs could be easily and affordably obtained.

14.2 Lung

The shortage of suitable donor lungs is similar, if not even more serious, than the shortage of hearts. The ISHLT/UNOS Registry reports approximately 1,200 lung transplants annually (Figure 2).[196] The most transplants occurred between 1995 and 1997, with a small but real decline in 1998.

In the United States, more than 3,000 patients await lung transplantation (LTx), and yet <1,000 lung transplants will be performed during the current year (of which approximately 20 will be from living donors) (Table VIII).[197] In the United States, the median waiting time for a lung (567 days) is more than double that for a heart (Table XII), and the waiting time for a heart and both lungs (740 days) is more than three times as long as the waiting time for a heart. The number of patients who die awaiting a lung is 10% annually (409 out of 4,056 in 1997) (Table XIII). Although annual mortality is 10%, a patient on the waiting list has a 30% chance of dying before obtaining a donor organ.[204] Patients with idiopathic pulmonary fibrosis are particularly at risk. The number who die awaiting combined heart and lungs exceeds 15% annually (57 of 374 in 1997) (Table XIII).

Arcasoy and Kotloff[204] provide data showing that the number of patients listed today for LTx in the United States has increased 8-fold since 1990, the number transplanted is up 3-fold, and the number who die while waiting is up 10-fold. In the United States, the discrepancy between the number of patients on the waiting list and the number who receive transplants is steadily increasing, as is the overall number of patients who die on the waiting list each year.[205] In the year 2000, the estimated discrepancy between those listed and those undergoing LTx will reach 2,000, and approximately 600 patients will die awaiting donor organs. The percentage mortality rate on the waiting list would probably have increased further were it not for improvements in managing patients with end-stage lung disease. Additionally, an almost certain tendency will occur to add patients' names to the waiting list at an earlier stage of their disease process, enabling them to remain stable longer and

TABLE XVII Number of patients waiting, transplanted, and dying on the lung transplantation waiting list in the Eurotransplant region,[a] 1991 to 1998

Year	Number of patients on waiting list on December 31	Number of transplants performed during the year	Number of patients who died on the active waiting list during the year
1991	90	71	NA
1992	141	109	NA
1993	203	119	NA
1994	227	138	NA
1995	224	125	NA
1996	204	154	71
1997	216	155	89
1998	224	228[b]	91

Source: Eurotransplant International Foundation Annual Report 1998.
[a]Eurotransplant region comprises Austria, Belgium, Germany, and the Netherlands.
[b]The significant increase in the number of transplants performed between 1997 and 1998 is considered a result of better use of available donors rather than of an increase in the number of donors.
NA, data not available.

TABLE XVIII Number of new patients added to the waiting list for lung and heart–lung transplantation in the United Kingdom, 1994–1999

	New registrations	Transplanted	Died on active waiting list
Lungs			
1994	162	115	19
1995	180	113	51
1996	168	117	50
1997	186	103	65
1998	145	92	68
1999[a]	137	79	38
Heart + Lungs			
1994	82	52	23
1995	101	58	30
1996	129	53	35
1997	86	44	34
1998	70	52	22
1999[a]	60	36	9

Source: UK Transplant Support Services Authority.
[a]Until August 10, 1999.

improving their chances of surviving until lung transplantation (however, this will compound the organ shortage by increasing the number waiting).

In the Eurotransplant region, data are similar, with 50% more patients added to the waiting list than who underwent LTx in the year 1998. The number of patients who died on the waiting list was equivalent to almost 40% of the number transplanted in the same period (Table XVII). Thirty-eight percent of the patients died within 90 days of going on the waiting list. Patients with pulmonary fibrosis had the highest mortality, closely followed by patients with PPH,[206] data that correlate well with the ISHLT worldwide data.[207] This high mortality occurred despite a gradual increase in the number of LTx performed annually, from 71 in 1991 to 228 in 1998.[198]

As in the United States, in Europe the discrepancy between the number of patients awaiting organs and those who receive them increases approximately 10% to 20% per annum. In Australasia, the shortage of organs remains equally acute (Table X).

In the United Kingdom, currently 207 patients await single or bilateral LTx, and 140 await a combined heart–lung transplant.[208] The ratio of patients added to the waiting list to those who receive transplants is a little less than 2 to 1 (Table XVIII).

Annually, the number of lung transplants performed worldwide, therefore, remains low, particularly in relation to the estimated overall number of patients who die from end-stage pulmonary disease. The leading indication for LTx, chronic obstructive pulmonary disease/emphysema (COPD), affects about 14 million persons in the United States. In 1998, the annual death rate for COPD and allied conditions was 41.3 per 100,000 persons, an overall mortality of 100,000 people.[209,210] The total economic costs of COPD morbidity and mortality in the United States are approximately $24 billion annually, of which direct treatment costs of COPD-related illness accounts for almost $15 billion. Ten percent of those with COPD account for >70% of all medical care costs, suggesting that LTx in these patients might be very cost effective.[211] Figures from Europe do not differ markedly and may show an even higher death rate.[212]

Although the prevalence and annual mortality of other conditions considered suitable for LTx, e.g., idiopathic fibrosis, PPH, and cystic fibrosis, are lower, evidence suggests that in many centers only a small percentage of affected patients currently receive consideration as potential candidates for LTx. The selection process relies on absolute or relative contraindications and on estimations of survival outcome after LTx. Excluding economic factors,

donor-organ scarcity plays the major role in limiting the more widespread application of LTx.

The ISHLT/UNOS Registry numbers grossly underestimate the potential demand for donor lungs because current age limits, organ shortage, and in many centers, other relative/absolute exclusionary criteria restrict programs from assessing the majority of people with end-stage lung failure and currently exclude all elderly (>55 to 60 years) patients with severe involvement of both heart and lungs.

Patients currently dying on the waiting list would obviously benefit from an unlimited supply of donor organs. In the United States, this group comprises approximately 400 to 500 patients annually. In the Eurotransplant region, 80 to 100 patients could benefit annually. According to data from the Registry, this number primarily includes patients with idiopathic fibrosis and PPH who have a high risk of dying while on the waiting list.

The indications for LTx could be widened to include patients currently denied LTx because of organ scarcity. This group includes those with lower survival prognoses after LTx, including potential candidates for retransplantation. Currently the 1-year survival rate for retransplantation is 50%,[213] and most patients are denied retransplantation on the basis that valuable donor organs should go to patients with better post-transplant prognoses.

The present waiting list simply reflects current recipient-selection policy. In the United Kingdom, 6,854 deaths occurred in 1997 from non-malignant pulmonary disease in patients aged 65 or younger, and 4,356 deaths occurred in patients aged 60 or younger. These patients represent a potential for LTx if an unlimited supply of donor organs were available. If older patients were considered, clearly the number would rise further. If liver XTx proved to be an option, patients with COPD who had α1-antitrypsin deficiency with advanced liver disease might become candidates for combined lung–liver transplantation.

In view of the current limited organ supply, replacement of both lungs is performed only when medically essential. If an unlimited number of organs were available, bilateral LTx could be performed in every patient who would medically benefit.

We conclude, therefore, that even with the present rigorous selection criteria for patients submitted for heart, lung, or heart–lung transplantation, a definite need exits for a new source of thoracic organs, and that this need is universal in all of the countries that perform these procedures. Furthermore, a new source would allow, and be followed by, enormous expansion in thoracic-organ transplantation procedures and might bring HTx or LTx to some countries that currently do not offer this therapy or that offer it only rarely.

15.0 APPENDIX 2: POTENTIAL APPROACHES TO DONOR SHORTAGE

15.1. Increased Human Cadaveric Donation

Increased availability of human cadaveric organs would clearly have an impact on the number of patients who could receive transplantation. We need improvement in the number of cadaveric donors that become available in most countries, even in those with relatively high rates of organ transplantation per million of population. In the various states within the United States, the various countries within Europe, and the various states within Australia, donation rates fluctuate widely by region. For example, in Australia, donation rates range from 9.5 to 24 per million.

At the end of 1989, the Organizacion Nacional de Trasplantes was created in Spain to optimize organ donation.[214] As a result, the annual number of organ donors increased continuously from 14.3 per million in 1989 to 31.5 per million in 1998. This organ donation rate is approximately double the figure elsewhere in the Western world. In Spain, the mortality rate of patients on the waiting list for HTx decreased to 7.1% and for LTx to 3.9% in 1998. This compares extremely favorably with figures reported from the Eurotransplant region, where the mortality rate for patients awaiting HTx was 21.4% and for those awaiting LTx was 23.9%. The Spanish estimate, however, that they continue to lose 22% of potential donors because the family fails to give permission to use organs.

Several reasons explain the success of the Spanish system, including paying specified physicians and nurses to identify and "acquire" potential donors at key hospitals, as well as some financial inducement to families of donors for consent to donation. (Personnel in U.S. centers, for example, in Pennsylvania, are currently studying financial incentives in the form of a "death grant" to pay funeral expenses. Recommending whether financial incentives be considered to increase the supply of donor hearts and lungs is beyond the scope of this report, but we recommend that the ISHLT consider it in more detail.)

Changes in laws in various countries could result in significant changes in donation rates. Introducing a "required request" law into several U.S. states, although ensuring identification of potential donors,

has not significantly affected the rates of donation. The effect of the "presumed-consent" law, which allows organ removal for transplantation from deceased persons who have not previously indicated that they do not wish to donate, has not been fully proven. Introduced in Belgium and Austria, the law resulted in a LTx rate as high as 7.6 patients per million in 1998 in Austria, with only 10 of 71 patients (14%) dying on the waiting list. In contrast, Germany, in which the law has not been introduced, had a LTx rate of 1.4 per million, with 49 of 200 patients (25%) dying on the waiting list. The potential benefit of introducing an "opt-out" or presumed consent law, however, remains uncertain. The study by Land and Cohen[215] could not find an obvious correlation between high organ removal rates and the existence of presumed-consent laws.

Elective ventilation of all potential organ donors simply to maintain life while inquiring about organ donation has also been proposed. A pilot study carried out in the United Kingdom in 1990 demonstrated that a policy of elective ventilation might double the number of identified potential donors.[216] However, in some countries, it remains illegal to ventilate a patient unless the individual patient's care medically indicates a need.

Nevertheless, even if organ retrieval could be doubled in every country that offers organ transplant services, which for a number of reasons is unlikely to happen, supply would remain insufficient to meet the potential demand. Researchers in several countries have made careful estimates of the total number of organs that would become available if the organs from every potential donor were acquired for transplantation, and even then, the supply would not meet the demand.[202] Only an estimated 4% of those who die in hospital are suitable as potential organ donors. The number of potential donors who become available each year is unlikely to increase significantly in many countries as recently introduced laws relating to driving (e.g., relative to blood-alcohol levels) and gun control take their effect.

15.2. Improvements in Medical Therapy

With regard to the heart, improvements in medical therapy continue to decrease disease progression and to improve survival for mild-to-moderate heart failure.[217] One-year survival in ambulatory patients referred for transplantation has improved from less than 50% 25 years ago to 80% in the past decade.[218] Survival is also improving in patients with more severe heart failure. A significant reduction in the number of patients submitted for HTx could occur if optimal heart failure therapy were used worldwide. Currently, this is not the case. Many patients referred for HTx have not previously been enrolled in a qualified heart failure management program. For example, many who might benefit from beta blockade or spironolactone have not been offered a trial of this therapy.

The therapies currently available for patients with advanced heart failure include angiotensin-converting enzyme inhibitors, with 10% to 20% of patients with resting circulatory compromise cannot tolerate these neurohormonal antagonists because of hypotension, particularly when serum sodium is low. Although clinical trials show a clear survival benefit of β-adrenergic blocking agents in decreasing progression of disease in patients with mild-to-moderate heart failure, such agents may be contraindicated in unstable patients with severe failure.[219] Such patients often require individualized therapy, which can include combinations of angiotensin-converting enzyme inhibitors, nitrates, hydralazine, angiotensin-receptor antagonists, and additional diuretic agents such as spironolactone, which improves survival in those carefully selected for stable renal function without hyperkalemia. Effective therapy in these patients clearly requires ongoing evaluation and adjustment outside of available algorithms.

Physicians currently debate the value of hemodynamic monitoring in redesigning effective therapy for patients who require frequent hospitalization for severe heart failure symptoms.[220,221] Trials of intermittent outpatient dobutamine infusions suggest increased mortality. Therefore, considerable doubt exists about the value of establishing clinics to provide intermittent or continuous outpatient infusions of inotropic drugs.[222] Multiple different approaches have been developed for advanced heart failure, but broad consensus exists on the value of enrolling patients into programs that provide education, activity counseling, and regular contact with experienced multidisciplinary staff.

We do not know the proportion of patients with low ejection fraction who would fail to respond to optimal heart failure management, if it were provided to them. At some centers, it remains easier to obtain recognition and referral to an expert surgical program than to the expert medical program that supports it. Nevertheless, we conclude that improved medical therapy, with the currently available drugs, would defer rather than negate the need for an increased source of donor hearts.

With regard to the lung, improvement in medical therapy has occurred for patients with PPH. Calcium antagonists have become standard therapy for responsive patients[223] and have proven their ability to improve life expectancy. More recently, patients unresponsive to calcium-antagonist therapy have received continuous intravenous prostacyclin, via portable pumps. Physicians have demonstrated prostacyclin's beneficial effect and the drug's use is encouraging,[224,225] although it may be difficult to predict which patients will respond and for how long.[226] Furthermore, this therapy is expensive and may not be available to some patients. Recent developments in PPH treatment include inhaled or subcutaneous infusions of prostacyclin analogues.[227] Data on long-term efficacy are pending. Although medical therapy for PPH has progressed during the past 10 years, attempts to improve the patient's condition by creating a beneficial atrial septal defect (ironically treating one defect, the disease process, by creating another defect, the atrial septal defect) illustrate its limitations.[228]

Antioxidant and anti-protease therapy may affect deteriorating lung function in patients with cystic fibrosis, bronchiectasis, lung fibrosis, and COPD, but it is too early to assess the extent of this impact.[229] α1-antitrypsin replacement therapy is currently under long-term investigation in patients with this deficiency. Whether this therapy can effectively stop the progression of COPD and prevent patients from becoming candidates for LTx remains unclear.[230] Improvements in drug therapy for such conditions as cystic fibrosis might well reduce the need for LTx in this group, but improved therapy for patients with advanced COPD or lung fibrosis is unlikely to substantially reduce the numbers awaiting LTx. A major change in lifestyle (e.g., a reduction in smoking) must occur for a significant percentage of the population before realizing a large impact on the number of patients awaiting donor lungs.

In summary, unless new drugs become available that effectively treat, or preferably prevent, the various disease processes that lead to end-stage pulmonary disease, optimal drug therapy is unlikely to significantly affect the number of patients referred for LTx.

15.3. Use of Sub-optimal Donors

Increased performance of heterotopic HTx might allow use of sub-optimal donor hearts (e.g., those with some coronary artery disease). For example, in Australia, only 50% of donors who have given consent have hearts acceptable for orthotopic HTx (A.M. Keogh, personal communication). However, this approach remains less than ideal because the problems of sub-optimal function and potential coronary artery "events" would be added to those of retaining the diseased native hearts, which include thromboembolism and arrhythmias.

The use of hearts from non-heart-beating donors has potential, but in the absence of a "cardioplegic solution" that protects or even reverses the myocardial injury that develops at the time of ceased cardiac function, this is not a significant option.

Using sub-optimal donors for LTx may also be considered, whether lungs come from non-heart-beating donors or from those with some degree of lung disease, particularly infection. In the United Kingdom, for example, only 20% to 30% of lungs offered for LTx are considered optimal.[231] Between 300 to 400 donor lungs could be used for LTx if management of the donor could be improved or if the criteria for lung donation were relaxed.

Increasing evidence suggests that more active management of donors would improve the number of lungs suitable for transplantation. Strategies to minimize injury to lungs in donors might include systemically blocking inflammation in all trauma patients,[232] justifiable because it would prevent or reduce acute respiratory distress syndrome in these patients. However, the therapeutic form that this would take remains uncertain. Even if a significant proportion of current, potential lung donors were rendered acceptable, the total number of lungs available for transplantation would remain well below the potential number of patients who might benefit from LTx.

Although not strictly sub-optimal donors, we might consider the use of cadaveric lobar transplantation. This technique allows use of a single lung for more than 1 transplant,[233] but as with using living donors (see Section 15.4), it is unlikely to contribute significantly to the overall management of patients with end-stage lung disease.

15.4 Use of Living Donors (Lung)

The use of living donors clearly has application only for patients in need of LTx, except with respect to the very small number of patients who might receive a donor heart from a patient undergoing combined heart–lung transplantation. This has become increasingly rare since establishing bilateral LTx.

Transplanting lobes from living donors (related or unrelated) is possible in infants and children with advanced lung disease. However, it is a major pro-

cedure for both recipient and donor and not without some morbidity for the donors, although this is less significant than initially anticipated.[234,235] Nevertheless, the possibility of donor-related complications exists, and, in the face of chronic rejection despite living-related donation, expansion of this approach seems limited. In addition, living donation presents an option only for smaller recipients, because donation of a whole lung would be deemed unjustified. Living donation will unlikely play a significant role in LTx in adults, and therefore this limits its potential as a source of donor lungs. It does, however, illustrate efforts to redress the scarcity of donor lungs for younger patients.

15.5 Implantable Mechanical Devices

During recent years, major improvements and developments have occurred in the field of cardiac implantable mechanical devices (e.g., ventricular assist devices). These devices have proved invaluable in "bridging" patients with advanced heart failure until human donor organs become available.[170–173] Ventricular assist devices can support patients longer than 1 year. However, the number of patients in whom these devices have functioned for that time remains relatively small, and therefore their truly long-term function remains uncertain.

All of the devices currently available require the patient to wear a battery belt around his or her waist and to change the batteries every few hours, unless the device is connected to a fixed electrical source. This not only significantly restricts life, but also necessitates passing a connecting lead through the patient's chest or abdominal wall, between the device and the power source. This constitutes a potential source of infection.

Researchers are currently testing devices that do not require a connecting lead, as power passes across the abdominal wall. However, the requirement for an external source of power remains, which requires periodic replacement. For a ventricular assist device to compete successfully with a transplanted heart, a power source must be developed that is small enough for insertion into the patient, either under the skin or within the chest or abdominal cavity. Furthermore, this power source should not require replacement more frequently than every few years. When this can be achieved, these devices will prove strong competition to heart transplants. However, improvements in ventricular assist devices to achieve these standards in the near future remain unlikely.

Nevertheless, the results currently obtained with mechanical assist devices in animals and humans are greatly superior to those obtained with xenografts in non-human primates. Mechanical assist device support is clearly preferable to cardiac XTx for bridging to allotransplantation, given the current results of experimental XTx (see 6.3). Furthermore, ventricular assist devices could fulfill the requirement for long-term cardiac support. Currently, we cannot conclude whether improved mechanical devices will ultimately offer a more successful solution to the need for cardiac replacement than will XTx.

Although development of implantable mechanical devices that act as artificial lungs progresses,[236–239] these devices remain in an early stage of development with no immediate prospect for widespread clinical application.

In the past several years, researchers have made progress in extracorporeal membrane oxygenation and report patient survival rates of 55% to 60% in treating acute respiratory distress syndrome.[240,241] As temporary support for a failing lung, this technique has the advantage of fairly easy application and may prevent further mechanical damage to the lung because it avoids the need for excessively high ventilation pressures. Extracorporeal membrane oxygenation will likely play an increasing role as a temporary bridging method until recovery of the failing lung or until availability of a donor organ. However, the technique has no potential to permanently replace the lung.

Trials of implantable devices designed to oxygenate the blood and remove carbon dioxide are now in progress, but these devices are not as efficient as external artificial lungs. Efficiency, biocompatibility, and anticoagulation remain significant hurdles. Temporary support, analogous to ventricular assist device bridging, and with similar limitations and complications, has recently been tested in sheep, and may soon be ready for initial clinical application. This technology may help bridge sick patients to allotransplantation or XTx and may help stabilize patients during a tolerance-inducing regimen. However, we are unlikely to see its efficacy for chronic organ replacement within the next 10 years.

15.6 Alternative Surgical Procedures

The results of alternative surgical procedures aimed at improving the function of hearts with dilated cardiomyopathy vary and remain under close investigation. At present, these procedures have a relatively limited application in patients with end-stage heart disease. Partial left ventriculectomy (the Batista operation) has not led to major clinical improvement for many survivors.[242] Cardiomyoplasty using skeletal muscle has not fulfilled its

promise and is not actively investigated in most centers treating heart failure patients.[243] Mitral valve repair for regurgitation that characterizes decompensation has been encouraging in a small series of patients but is not currently considered for larger heart failure populations.[244] Biventricular pacing may prove beneficial in selected patients and is under clinical investigation.[245,246] Investigations into therapy with transmyocardial laser have thus far excluded patients with severe left ventricular dysfunction but may lead to improvement in patients with intractable angina pectoris.[247]

Revascularization procedures or left ventricular aneurysmectomy may help some patients with coronary artery disease who are of particularly high surgical risk, but a limited number of patients will benefit from this approach.

Surgeons introduced lung-volume reduction surgery into clinical practice with considerable enthusiasm. In ideally-selected patients with marked hyperinflation and pronounced heterogeneity of disease, significant improvement in lung function and quality of life can be achieved, which in some patients defers or even eliminates the need for LTx.[248] However, the surgery is not without risk, and its long-term functional benefit varies. Even at best, it does not replace lung function as effectively as LTx, although late complications of the procedure are minimal when compared with those of long-term immunosuppression. Perhaps its most beneficial effect is in the population currently considered above the transplant age (>65 years), who make up a significant percentage of the pool of patients with pulmonary failure. At present, approximately 700 patients are screened annually for lung-volume reduction surgery in the NETT trial (G. Weinmann—personal communication). Presumably, many of them might be considered for LTx if XTx provided an unlimited number of donor organs.

Chronic thromboembolic pulmonary hypertension is an underdiagnosed disease that, in carefully selected patients, is curable (or can be greatly alleviated) with pulmonary thromboendarterectomy.[249] However, it is not an indication for LTx unless peripheral disease has led to severe pulmonary hypertension.

15.7 Gene Therapy

Researchers are exploring gene therapy techniques to treat atherosclerosis, myocardial infarction, angina pectoris, and familial hypercholesterolemia,[250] but it will be many years before gene therapy has an impact on the number of patients referred for HTx.

As a potential solution for advanced lung disease, gene therapy remains in a relatively primitive stage of development. To date, gene therapy for patients with cystic fibrosis has demonstrated only limited success.[251] The main problems are limited efficiency of the viral vectors or liposomes and the presence of either immunologic or inflammatory reactions. However, initial clinical studies involving 100 patients demonstrated positive transfer of genes. It seems certain that this form of therapy could impact treatment of cystic fibrosis in the long-term, but in the medium-term (10 to 20 years) its impact is uncertain. Gene therapy techniques may help patients with pulmonary fibrosis and COPD, particularly those with α1-antitrypsin deficiency. However, it remains unclear whether gene therapy will effectively stop the progression of emphysematous disease and thus prevent patients from becoming candidates for LTx.[252]

15.8 Cellular Augmentation and Tissue Engineering

Culturing cardiomyocytes or skeletal muscle cells and introducing them into a failing myocardium to augment function is in its infancy, even in experimental models, and the role cellular augmentation might play in future clinical therapy remains uncertain.[253] Tissue engineering techniques to develop new organs remain even less advanced.[254]

15.9 Xenotransplantation

Successful use of pig organs would provide an unlimited supply of donor organs, available whenever required. This compares with using mechanical assist devices in that the organs would be available instantly (or within hours). This would have a major impact on the logistics of thoracic-organ transplantation because patients would not be confined to intensive care units for weeks or months while awaiting an organ, and surgical teams would not have to travel long distances at inconvenient times to retrieve donor organs as an emergency. The vast majority of transplants could be scheduled, and only an occasional procedure would need to be performed as an emergency.

A normally functioning pig heart would have advantages over a mechanical assist device: for example, no risk of thrombosis on moving mechanical structures and no risk of other mechanical failures. However, the risk of rejection would offset these advantages, as would complications of long-term immunosuppressive drug therapy, if required. Xenotransplantation currently remains in a significantly more primitive developmental stage than that

of mechanical assist devices. Survival of discordant cardiac xenografts in large animal models is currently measured in days or weeks, whereas survival of patients supported by mechanical assist devices is measured in months or even years. Nevertheless, if XTx could be achieved successfully, particularly if immunologic tolerance could be induced, this form of therapy probably offers the most complete solution to treating patients with end-stage heart disease unresponsive to other forms of therapy.

The potential of XTx to fulfill the need for donor lungs is comparable with its potential to fulfill the need for hearts (as outlined above). In the absence of an equivalent implantable mechanical device to support failing lungs, we could argue an even greater urgency for XTx in lung replacement than in heart replacement.

Adequate respiratory function and hemodynamics have been demonstrated after unilateral orthotopic transplantation of a pig lung into an immunodepleted baboon, although the duration of observation was limited to only a few hours.[69] As yet, researchers have not weaned an animal supported by a pig lung from a ventilator after transplantation. Xenotransplantation, therefore, appears less likely to overcome the limitation of donor lungs than that of donor hearts within the next few years.

15.10 Summary

Many thousands of patients will require some form of thoracic organ replacement. Approaches involving gene therapy, cellular augmentation, and tissue engineering remain in very primitive states of development. Increasing the number of donor thoracic organs that become available, anticipated improvements in medical therapy, and alternative surgical procedures (e.g., mitral valve repair for dilated cardiomyopathy or lung-volume reduction for COPD) may make a small impact on the number who require thoracic-organ transplantation. In the medium term, further developments in implantable mechanical devices or major advances in XTx represent the most likely potential solutions.

16.0 APPENDIX 3: KEY STEPS IN DEVELOPING REGULATORY GUIDELINES

1. 1993—Ethics Committee of the Transplantation Society. Human xenotransplantation. Position paper published in Transplant Soc Bull 1993;1:8.
2. 1995—Nuffield Council on Bioethics (UK). Animal-to-human transplants: the ethics of xenotransplantation. Report published in London, 1996.
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6. 1996—U.S. Department of Health and Human Services, Public Health Service. Draft guidelines on infectious disease issues in xenotransplantation. Federal Register 61(185):49920–32.
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21. 1999—UK Xenotransplantation Interim Regulatory Authority. Draft report of the infection surveillance steering group of the UKXIRA.
22. 1999—U.S. Department of Health and Human Services, Public Health Service. Guidance for industry: public health issues posed by the use of non-human primate xenografts in humans, 1999.
23. 1999—U.S. Department of Health and Human Services, Public Health Service. Guidance for industry: precautionary measures to reduce the possible risk of transmission of zoonoses by blood and blood products from xenotransplantation product recipients and their close contacts, 1999.
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