Projektbericht

Research Report

Update-Report: Baseline evaluation of the scientific state of the art in XTP of organs

Increasing Public Involvement in Debates on Ethical Questions of Xenotransplantation

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Update-Report: Baseline evaluation of the scientific state of the art in XTP of organs

Increasing Public Involvement in Debates on Ethical Questions of Xenotransplantation

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Report

Studie im Auftrag der Europäischen Kommission
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Fraunhofer Institute for Systems and Innovation Research
Karlsruhe, Germany

Contact:

Bärbel Hüsing
☎: +49/721/6809210
email: sb@isi.fhg.de

Contents

1. Goals of the Report

The project "Increasing Public Involvement in Debates on Ethical Questions of Xenotransplantation (XENO)[1]" has the goal to find out to which extent the instrument of the Neo-Socratic Dialogue appears suitable for discussing ethical aspects of xenotransplantation in public debate. This analysis is carried out in parallel in Austria, Spain and Germany. The project comprises the following steps:

1. Characterization of public debate of xenotransplantation in the three countries investigated,
2. Monitoring of the international xenotransplantation development,
3. Country-specific design and organisation of Neo-Socratic Dialogues,
4. Realization and parallel evaluation of two Neo-Socratic Dialogues per country,
5. Country-specific and cross-country assessment of the experiences with and results from the Neo-Socratic Dialogues,
6. Information of relevant stakeholders about the project results.

This report presents the results of the second working step. It supports the evaluation of the public xenotransplantation debate in Austria, Spain and Germany (i. e. the countries investigated in the XENO project) by providing background information on the international developments in xenotransplantation. For this purpose, the preliminary report was updated and complemented by an additional chapter on international activities related to xenotransplantation and their output in terms of reports, opinions or regulations.

Goals of this report are

- to give an overview of international organ donation and transplantation,
- to summarize the scientific-technical achievements of xenotransplantation research obtained up to now,
- to give an overview of xenotransplantation-related activities of international bodies and committees.

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[1] Contract No. HPRP-CT-2001-00013

2. Methods and Data

The methods used to obtain the relevant information for this report are

1. analysis of scientific and grey literature, reports and policy papers,
2. searches of internet sources,
3. previous studies on xenotransplantation carried out by our institute which included participation in symposia, conferences and workshops on xenotransplantation,
4. interviews with xenotransplantation experts.

3. Overview of organ donation and organ transplantation internationally

During the past three decades transplantations of organs, tissues and cells have become routine surgical procedures. Irreversibly damaged organs, tissues and cells are replaced by functional ones. In many cases transplantations are life-saving, e. g. liver transplantation after fulminant hepatic failure, bone marrow transplantation after leukemia or skin transplantation after severe burns. In addition, the patient's quality of life can be substantially improved, e. g. in the case of kidney transplantation which makes the transplant recipient independent of dialysis, or in the case of cartilage transplantation after joint injury which makes full mobility without pain possible.

The following organs are transplanted: heart, kidney, liver, lung, pancreas and small intestine. Tissues transplanted comprise corneas, skin, blood vessels, bone, cartilage. Moreover, cells such as pancreatic islets and blood stem cells are transplanted.

In Europe, the USA and Canada, and Australia a total of nearly 42,000 organs were transplanted in 2001 (Table 3.1). More than the half of these transplantations were kidney transplantations, followed by liver transplantations (nearly 11,000), hearts, lungs and pancreas. Small intestines are very rarely transplanted (126 transplantations), most of them in the USA. The transplantation of kidneys, hearts and livers is surgical routine today while lung transplantation is in the process of achieving this phase.

The number of organs transplanted per million inhabitants differs largely from country to country: leading countries with 80 to 90 organ transplantations per million inhabitants are Spain, Austria and the USA (Table 3.2).

Table 3.1: Overview of organ transplantations (absolute numbers) in 2001

Country	Kidney*	Liver	Heart[+]	Lung[++]	Pankreas	Bowel	Total
EU-15 total	**10.644**	**4.844**	**1.895**	**738**	**492**	**14**	**18.627**
USA	8.859	5.177	2.202	1.054	884	112	18.288
Germany	1.964	757	409	139	200	3	3.472
Spain	1.893	972	341	143	56		3.405
France	1.921	803	342	117	53	2	3.238
Italy	1.447	792	316	62	61	5	2.683
UK	1.333	675	198	92	41	2	2.341
Canada	661	389	164	124	33		1.371
Poland	843	103	129		17		1.092
Belgium	358	201	84	46	21		710
Austria	362	128	66	57	19	1	633
Australia	328	120	68	74	21		611
Portugal	359	184	17	1	4		565
The Netherlands	337	107	37	27	23	1	532
Czech Republic	310	58	49	10	20		447
Sweden	188	102	25	21	5		341
Switzerland	156	88	38	25	12		319
Turkey	162	107	27				296
Hungary	259	19	9	0	7		294
Finland	165	38	13	4			220
Norway	125	37	29	13	12		216
Denmark	121	32	31	29			213
Ireland	113	35	11	0	9		168
Greece	74	18	5	0			97

Croatia	61	20	9	0			90
Slovenia	47	9	4	0			60
Estonia	30	1		0			31
Luxemburg	9						9
Bulgaria	4						4
Slovacia							0
Lithuania							0
Cyprus							0
Total	**22.489**	**10.972**	**4.623**	**2.038**	**1.498**	**126**	**41.746**

* from brain-dead donors,
\+ including heart-lung transplantations,
++ unilateral and bilateral

Source: http://www.msc.es/ont/ing/f_data.htm, accessed Feb. 11, 2003

Table 3.2: Overview of organ transplantations per 1 mio. inhabitants in 2001

Country	Kidney*	Liver	Heart+	Pankreas	Bowel	Total
Spain	46,0	23,6	8,3	1,3		79,2
Austria	44,8	15,9	8,2	2,4	0,1	71,4
Belgium	35,8	19,7	8,2	2,0		65,7
USA	33,0	19,3	8,2	3,2	0,4	64,1
Portugal	34,9	18,4	1,7	0,4		55,4
France	32,0	13,4	5,7	0,9	0,0	52,0
Italy	25,0	13,7	5,5	1,1	0,1	45,4
Ireland	30,2	9,4	2,9	2,4		44,9
EU-15 total	**28,1**	**12,0**	**4,5**	**1,5**	**0,1**	**44,5**
Norway	27,7	8,2	4,0	2,7		42,6
Czech Republic	30,1	5,6	4,8	1,9		42,4
Finland	31,9	7,3	2,5			41,7

Switzerland	22,0	12,2	5,3	1,7		41,2
Germany	23,9	9,2	5,0	2,4	0,0	40,5
Canada	21,3	12,5	5,3	1,1		40,2
UK	22,6	11,4	3,4	0,7	0,0	38,1
Sweden	21,1	11,4	2,8			35,3
Denmark	22,3	5,9	5,7			33,9
The Netherlands	21,1	6,7	2,3	1,4	0,1	31,6
Slovenia	23,5	4,5	2,0			30,0
Hungary	25,9	1,9	0,9	0,7		29,4
Poland	21,8	2,7	3,3	0,4		28,2
Australia	16,9	6,2	3,5	1,1		27,7
Luxemburg	22,5					22,5
Estonia	21,4	0,7				22,1
Croatia	13,9	4,5	2,1			20,5
Greece	7,4	1,8	0,5			9,7
Turkey	2,4	1,6	0,4			4,4
Bulgaria	0,5					0,5
Slovacia						0,0
Lithuania						0,0
Cyprus						0,0
Total	**24,4**	**9,5**	**4,1**	**1,5**	**0,1**	**34,2**

* from brain-dead donors,
\+ including heart-lung transplantations

Source: http://www.msc.es/ont/ing/f_data.htm, accessed Feb. 11, 2003

Table 3.3: Organ donations in selected countries in 2001

Country	Number of organ donors	Organ donors per million inhabitants	Multiorgan donors
Spain	1335	32.5	84.4%
Austria	191	23.7	77.8%
USA	6081	22.6	n. a.
Belgium	222	21.6	47.7%
Portugal	202	20.2	78.7%
R.Ireland	68	18.2	81%
France	1066	17.8	n. a.
Latvia	41	17.8	n. a.
Italy	988	17.1	n. a.
Finland	88	17	48.9%
Czech.Rep	172	16.7	48.3%
Malta	6	15	100%
Norway	65	14.4	83%
Hungary	137	13.7	19%
Canada	420	13.5	n. a.
Switzerland	95	13.2	76.8%
Germany	1073	13.1	77%
United Kingdom	777	13.1	83%
Denmark	70	12.9	74.3%
Luxemburg	5	12.5	100%
Sweden	108	12.1	75.9%
The Netherlands	187	11.7	61.4%
Poland	450	11.6	38.4%
Slovenia Rep.	23	11.5	85%
Estonia	14	10	7.14%
Australia	180	9.3	81%
Israel	59	9	37.2%
Croatia	32	7.3	62.5%
Greece	32	3.2	n. a.
Turkey	89	1.3	n. a.
Romania	21	0.95	76.19%
Bulgaria	2	0.26	n. a.

n. a. data not available

Source: Organización Nacional de Trasplantes; http://www.msc.es/ont/ing/data/organo.asp?O=2&DO=DONORS&aO=2001; accessed on October 15, 2002

The frequency of organ transplantations depends on – among other factors – the frequency of organ donation. The number of organ donors differs largely from country to country, as well as the share of multi organ donations (Table 3.3). In Europe, Spain, Austria and Belgium/Luxemburg hold the leading positions with 32.5 to 23.7 donors per 1 mio. inhabitants. As a consequence of the gap between demand and supply of donated organs, the waiting times for an organ transplantation have become longer. The longest waiting times exist for kidney- and heart-lung transplantations, the waiting times for heart transplantations

are the shortest. Worldwide, several thousand patients die while still on the waiting list because no suitable organ was available in time. This holds especially true for patients waiting for a heart or a lung, because for these organs there are hardly any live-saving alternatives to organ transplantation.

Due to progress in modern transplantation medicine very good results regarding the organ survival in the transplant recipient[2] are achieved (Table 3.4). It must, however, be differentiated regarding the different organs. The best results are achieved with kidneys: more than 90 % of the transplanted organs function one year after transplantation surgery, and more than 80 % still three years after surgery. The 3-year survival rate covers a range of more than 40 % (heart/lung transplantation) to more than 80 % (kidney). Long-term loss of transplanted organs is mainly due to chronic rejection, to the death of the transplant recipient and the relapse of the disease which caused the organ damage in the first place.

Table 3.4: Survival rates of allotransplants one and three years after transplantation in the USA, 1996-2001

Transplanted organ	Share of surviving organs in % of all transplanted organs[3]	
	after one year	after three years
Kidney / Pancreas	92.0	83.6
Kidney	90.9	81.4
Heart	84.7	77.3
Liver	81.6	73.0
Pancreas	79.2	60.7
Lung	77.0	57.4
Intestine	66.1	46.0
Heart / Lung	61.8	42.9

Source: Organ Procurement and Transplantation Network, http://www.optn.org, accessed April 20, 2004. Based on OPTN data as of April 9, 2004

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[2] On average, the patients' survival rates are even higher than the organ survival rates.

[3] Kaplan-Meier Graft Survival Rates; One year survival is based on data from transplantations performed in the USA between 1999-2001, and 3 year survival is based on 1996-1999 transplants.

4. State of the art in science and technology of xenotransplantation

4.1 Overview

Xenotransplantation is the transplantation of living cells, tissues and organs across species borders (Beckmann et al. 2000; Cooper et al. 1997; Cooper et al. 2000b; Hüsing et al. 1998; Hüsing et al. 2001; The Advisory Group on the Ethics of Xenotransplantation 1996). In the context of this report, xenotransplantation is understood as the transplantation of animal organs, mostly from pigs as source animals, to humans with the aim of treating diseases which are due to the irreversible loss of organ, tissue or cell function.

If animal organs could be transplanted successfully into humans, xenotransplantation could contribute to the solution of many problems of today's transplantation surgery. It could have the following advantages:

- *"Infinite" supply of organs according to organ demand.* The most severe problem of today's transplantation surgery is that the demand for donor organs is significantly higher than the number of donated human organs. As animals as organ source could be bred according to graft demand, xenogenic organs could be supplied to every patient in need of an organ transplantation. This could have the following desirable consequences:
  - saving the lives of patients who would otherwise die while waiting for an organ,
  - improving the organ recipient's quality of life,
  - no need for waiting lists any longer,
  - reduced psychological stress for patients and their families,
  - no demand for sale of human organs any longer.
- *Organ allocation solely based on medical criteria.*
- *Planned surgical procedures.* Organ transplantations could be planned beforehand and would no longer be emergency procedures. This could have the following desirable consequences:
  - improved clinical outcome,
  - reduced stress for patients, their families and the medical staff involved.
- *Reduced problem with brain death concept.* The ethical and legal problems associated with the brain death concept could be reduced, and also the psychological stress for relatives and medical staff.

These advantages could be realised within the established system of transplantation surgery. Xenotransplantation therefore seems to be an option which neatly fits into the existing transplantation system and "only" requires the changing of the organ source. Especially if the xenotransplantation of cells and tissues is considered, it offers the potential for expansion of transplantation medicine to the treatment of diseases and disorders which do not fall into the traditional surgery field (e. g. Parkinson's disease, diabetes).

Although xenotransplantation research dates back several decades, several scientific-technical hurdles must be cleared before xenotransplantation may be applied in the clinical practice:

- Control of xenograft rejection
- Physiology
- Risks of infection
- Genetic modification of source animals (pigs)
- Identity, psychological impacts
- Survival and quality of life

The present state of the art regarding these aspects will be described in the following chapters.

4.2 Control of xenograft rejection

Even in allotransplantation, the grafted organ is normally recognized as "foreign" by the patient's immune system and is rejected. In order to reduce this immune reaction, organ donor and transplant recipient must be matched immunologically, and the transplant recipient must be treated life-long with immunosuppressive drugs (Dumont 2001). These drugs usually have severe side effects, such as a higher probability of getting infectious diseases and cancer. Nevertheless, with the help of modern immunosuppressive drugs, the organ survival rate has improved considerably over the last decades. Depending on the organ, up to 80 % of the transplanted organs survive longer than one year and more than 40-80 % longer than three years (table 3.4). However, most organs are lost during events of chronic rejection which cannot be controlled sufficiently in allotransplantation (figure 4.1).

The immunological processes which underlie the rejection of xenografts are more complex and different from the rejection of allografts, and are less well understood (Cooper 2003; Cooper et al. 2002a; Cooper et al. 2002b; Council of Europe 2003; Dooldeniya et al. 2003; Platt 2003). Figure 4.1 gives on overview of the different immunological processes involved. As can be seen from figure 4.1, at least two additional rejection mechanisms, hyperacute

rejection and delayed rejection (also termed acute vascular rejection), become effective in xenograft rejection. It is assumed that – in analogy to allograft rejection – cellular and chronic rejection should also occur in xenograft rejection, but it has not yet been possible to study these mechanisms thoroughly in the xenogeneic model because the organs do not survive long enough in their host to investigate these processes.

Hyperacute rejection is mediated by natural antibodies that bind to the graft and then activate a powerful cascade of molecules called the complement system, which finally leads to destruction of the target. Natural antibodies are directed to galactose _-1,3 galactose structures, which are created by an enzyme _-1,3 galactosyltransferase (GGTA1) (Roos et al. 2002). Strategies to overcome hyperacute rejection aim at masking the galactose _-1,3 galactose targets for the natural antibodies, at depleting the natural antibodies, and at modifiying the complement activity. In 1995, a major breakthrough regarding hyperacute rejection was achieved: Hyperacute rejection can be overcome if organs from transgenic source animals are transplanted which express human complement regulatory proteins, such as human decay accelerating factor (hDAF, CD55), membrane cofactor protein (MDC, CD46), or protectin (CD59), or combinations thereof.

Table 4.1 gives a (non-exhaustive) overview of survival rates and survival times achieved in transgenic pig-to-non human primates xenotransplantation models. The results can be summarized as follows:

- Hyperacute rejection can be overcome in non-human primates if organs from pigs transgenic for human complement regulatory proteins are transplanted. hDAF is the complement regulator, that has been studied most frequently, but data from pigs transgenic for CD46 (Loveland et al. 2004) and CD59 (Lorenz et al. 2002; Niemann et al. 2001b) are also available. Combinations of different human complement regulatory proteins do not seem to offer significant improvements in the control of hyperacute rejection over the use of only one type of complement regulatory protein (Cowan 2000). However, additional experiments are underway to test the combination of *different* control strategies (Costa et al. 2002), especially the combination of human complement regulatory proteins with a knock-out of the α1-3 galactosyltransferase gene. Results from mouse models are encouraging (Cowan et al. 1998), and meanwhile the technologies are in place to introduce these genetic modifications also into pigs (Costa et al. 2002; Dai et al. 2002; Lai et al. 2002; Phelps et al. 2002; Platt 2002; see also chapter 4.5). Double knock-out pigs for this gene locus have recently been created (BioTransplant Incorporated 2003; Phelps et al. 2002; PPL Therapeutics 2002), and first promising data from BioTransplant Inc. and Immerge BioTherapeutics were presented at the American

Transplant Congress in Washington, June 2003, showing over two-month survival of a life-supporting kidney graft and a heart graft[4].

- Maximum survival times achieved so far for life-supporting xenografts are 78 days for kidney, 39 days for heart, and 8 days for liver. If the organ is transplanted in such a way that it does not fulfill life-supporting functions, the survival time of a xenogeneic heart was extended to 113 days. These survival times were only achieved in very few animals, but were significantly shorter in the majority of the test animals, and they stay far behind the survival times that can be achieved in allotransplantation (compare table 3.4). In the first experiments performed in the 1990s, heavy immunosuppression had to be applied, and the animals suffered severely from side effects of this immunosuppression. These immunosuppression protocols are not seen as suitable for use in human patients. In more recent experiments, carried out in the 2000s, improved immunosuppression regimes are being tested (see e. g. Asano et al. 2003; Ashton-Chess et al. 2004; Cozzi et al. 2003a; Cozzi et al. 2003b). They, however, do not prolong the graft function or graft survival significantly over the periods achieved in the first experiments.
- The lack of success in prolonging the graft survival times significantly beyond the durations already achieved in early experiments with transgenic grafts makes evident that overcoming hyperacute rejection is not sufficient in order to apply xenotransplantation in the clinic. As a consequence, research efforts are now directed to better understanding the mechanisms which determine graft failure and rejection after hyperacute rejection has been overcome.

While the majority of XTP research is focussed on kidney and heart transplantations (Ogata et al. 2004; Pham et al. 2004), few investigators have also begun to probe the possibility of pulmonary xenotransplantation. However, despite recent progress, lung xenotransplantation lags behind kidney and heart xenotransplantation, and clinical pulmonary xenotransplantation is not yet in sight (Cantu et al. 2004; DeMeo et al. 2001).

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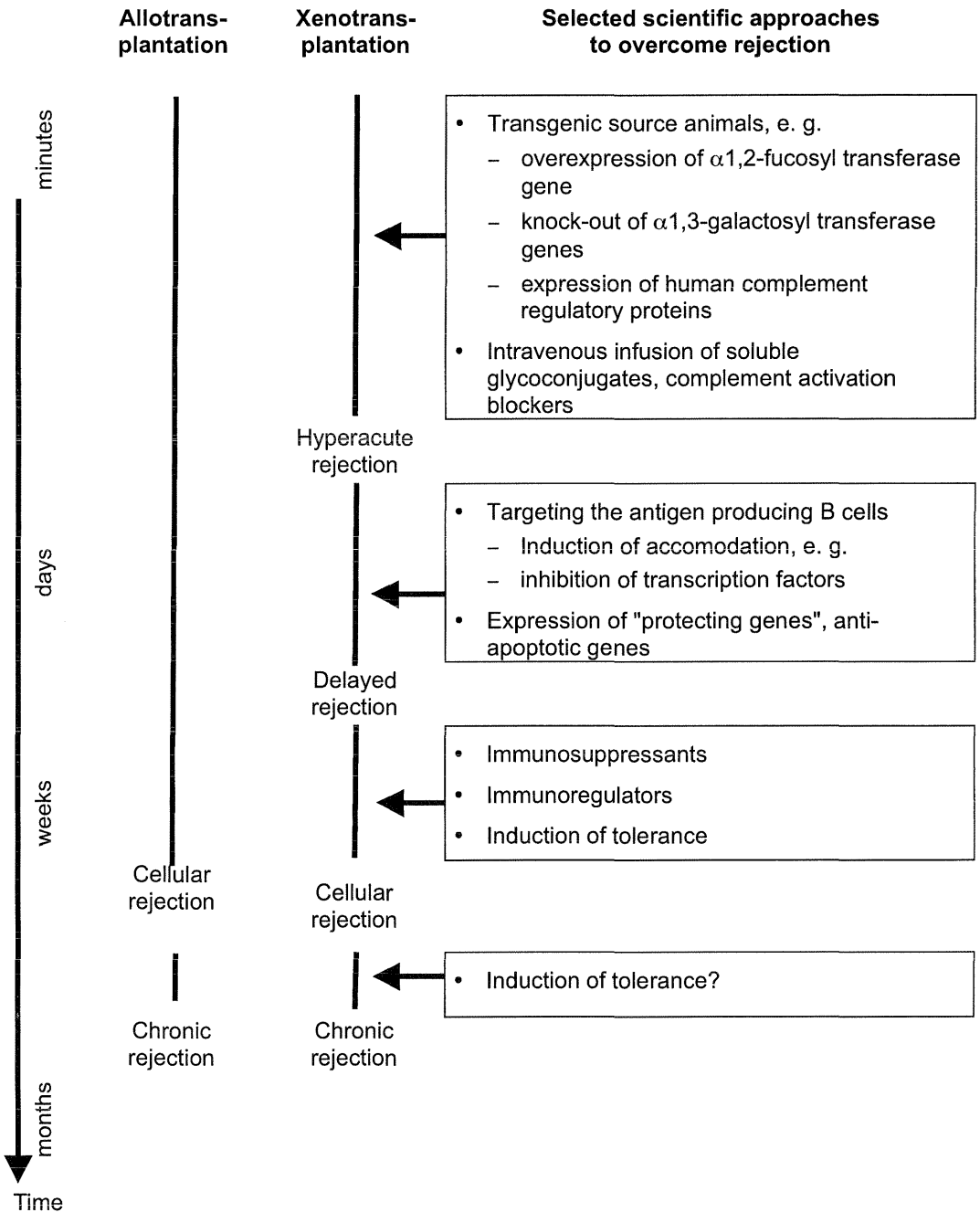
[4] http://www.immergebt.com/our_research/index.php, accessed April 21, 2004

Figure 4.1 Immunological processes involved in the rejection of allogenic and xenogenic organs



Source: de Wit 2001, modified

- If hyperacute rejection is overcome, additional rejection mechanism become effective which are different from known mechanisms in allotransplantation. The next immune reaction that must be controlled is delayed xenograft rejection (also termed "acute vascular rejection" or "acute humoral rejection"). After a phase of rapid progress, due to the ability to control hyperacute rejection, now a phase of slower progress has begun. It again requires intensive basic research into the mechanisms of the rejection processes. This is predominantly addressed in organ perfusion models, not in living animal models. It begins to emerge that the delayed xenograft rejection represents a spectrum of various rejection mechanisms that differ in components and mechanisms. Natural as well as elicited antibodies, complement and coagulation factors play a role in this rejection process (Dorling 2003; Mollnes et al. 2003; Schuurman et al. 2003). Strategies are being developed which aim at introducing additional genetic modifications into the source animal in order to overcome also delayed xenograft reaction (e. g. Bach et al. 1997; Soares et al. 1998). However, no assessment is possible at the moment whether these strategies will be successful and sufficient in controlling xenograft rejection (Cooper et al. 2002a; Cooper et al. 2002b).
- Acute cellular rejection follows delayed xenograft rejection. Knowledge of this mechanism remains scarce because it could not yet be studied in detail. At the present level of knowledge, it seems to be similar to that seen in allograft rejection (Schuurman et al. 2003), but more vigorous as demonstrated by the failure of several immunosuppressive protocols which are effective in allografts to significantly prolong xenograft survival. Induction of xenospecific T- and B cell tolerance and donor-specific immunotherapies are being discussed as possible options to overcoming this barrier (Sebille et al. 2003).

Therefore, many scientists are critical about whether it will be possible to control all rejection mechanisms by the combination of genetic modifications of the source animals and immunosuppressive drugs. On the one hand, there are still technical restrictions which and how many genetic modifications can be introduced into the porcine genome. On the other hand, it cannot be ruled out that some of these modifications will have negative or even lethal effects on the source animal, and therefore cannot be used.

Another option which would be of major importance for allotransplantation as well as xenotransplantation is the induction of tolerance in the transplant recipient. However, this option is also still in an early stage of development (Check 2002; Greenstein et al. 1997; Sachs 1998; Sachs et al. 1995; Waldmann 1999; Wekerle et al. 2001).

Table 4.1: Survival time of non-human primates which received xenografts from transgenic pigs

Organ	Xenograft life-supporting	Source animal	Recipient	Trans-planted animals	Survival time of recipient (days)		Remarks	Source
					Median	Max.		
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	7	13	35	Recipients not splenectomized, triple immunosuppression	Cozzi et al. 2000
		hDAF transgenic pig		7	39	78	Recipients splenectomized, triple immunosuppression, recombinant erythropoetin	
		pig		7	0	30		
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	13	21.5	51	Recipients splenectomized, triple immunosuppression, but reduced cyclophosphamide	Cozzi et al. 2003b
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	5	43	53		Schmoeckel et al. 1999a
		pig		5	5 h	30		
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	7	13	35		Zaidi et al. 1998
		pig		6	6.5	30		
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	9		68	Triple immunosuppression	Loss et al. 2000
		pig		8		11		
Kidney	yes	pig transgenic for CD55, CD 57 and a-1,2-fucosyltransferase (H-transferase)	Baboon	8	3	5	no immunosuppression	Cowan 2000
		pig transgenic for CD 55 and H-transferase		2		30 h		
		pig		4		< 1 h		

Table 4.1: Survival time of non-human primates which received xenografts from transgenic pigs (continued)

Organ	Xenograft life-supporting	Source animal	Recipient	Trans-planted animals	Survival time of recipient (days)		Remarks	Source
					Median	Max.		
Heart	no	hDAF transgenic pig	Cynomolgus monkey	8	5,1	5,25	no immunosuppression	Cozzi et al. 1997
		pig		10	1,6	4,2		
		hDAF transgenic pig		10	40	62	with immunosuppression	
		pig		5	55 min	3 h		
Heart	no	hDAF transgenic pig	Baboon	9	26	99		Bhatti et al. 1999
		pig	Baboon	5	5	10		
Heart	no	CD46 transgenic pig	Baboon	10	76	113	Complex immunosuppression	McGregor et al. 2003
Heart	no	pigs	Macaca mulatta	5	60 min	6	Control: Immunosuppression with cyclosporine, cyclophosphamide, steroids	Guo et al. 2003
				4	11,5	13	as above, plus complement depletion through cobra venom factor	
Heart	yes	hDAF transgenic pig	Baboon	1	-	39		Vial et al. 2000
Heart	yes	hDAF transgenic pig	Baboon	6	1,1	25	Baboons non-splenectomized, improved immunosuppression	Brandl et al. 2003
Heart	yes	hDAF transgenic pig	Baboon	10	2,5	9		Schmoeckel et al. 1998; Schmoeckel et al. 1999b

Table 4.1: Survival time of non-human primates which received xenografts from transgenic pigs (continued)

Organ	Xenograft life-supporting	Source animal	Recipient	Trans-planted animals	Survival time of recipient (days)		Remarks	Source
					Median	Max.		
Liver	yes	hDAF transgenic pig	Baboon	2	6	8		Ramirez et al. 2000
		pig		3		< 12 h		
Liver	yes	hDAF transgenic Pig	Baboon	2	6	8	Recipients splenectomized and immunosuppressed	Sanchez et al. 2003
		pig		4	-	massive damage after 2 hours		

4.3 Assessment of the risk of infection

Although it is known from allotransplantation that allotransplant recipients have a higher risk of infection than the average population, the risk of infection inherent in xenotransplantation was perceived relatively late. The first warnings addressed the use of non-human primates as source animals because they most likely pose a larger risk to humans than pigs. While in Europe xenotransplantation research focussed on the use of pigs as source animals due to infection and ethical reasons, in the USA the use of non-human primates as source animals was still taken into consideration. However, in 1999, the FDA excluded non-human primates as potential source animals (U. S. Department of Health and Human Services et al. 1999).

Since the mid-1990s concern has been expressed over the microbiological safety of porcine xenografts (Chapman et al. 1995; Fishman 1994; Michaels et al. 1994). The risk of infection is due to several factors:

- *Severe immunosuppression of the xenograft recipient*, thus rendering him at least as susceptible to infections as in allotransplantation.
- *Infection with known porcine pathogens* which might be transmitted with the porcine organ. Several bacteria, fungi and parasites are known which are pathogenic both in pigs and in humans, and which can be transferred between these species. A comprehensive review has been published by Muir et al. 2001). In addition, several viruses are known which can cause severe diseases if transmitted from pigs to humans, among them influenza virus, a picornavirus causing foot and mouth disease, rhabdoviruses (de Wit 2001). Studies of recipients of historic xenotransplants have provided evidence that xenograft-related infections of some recipients with simian foamy virus, baboon endogenous retrovirus, baboon cytomegalovirus and herpesviruses had occurred (Allan et al. 1998; Michaels et al. 2001; Michaels 2003). Experts are confident, however, that most of these pathogens can be successfully excluded from herds of source animals[5] if they are bred under specific pathogen free conditions and existing guidelines are closely complied with. It has been demonstrated in a health monitoring program that more than 80 potential pathogens could be excluded from nine cohorts of pigs which had been reared in a specific bioexclusion facility as potential xenograft source animals (Tucker et al. 2002).

  Under these circumstances, the risk of introduction of infection via contamination of the graft (e. g. during harvesting and surgical procedures) might exceed the risk of transfer of known pathogens via xenotransplantation (Chapman 2003; Tucker et al. 2004).

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[5] This may, however, remain difficult for pathogens which are transmitted congenitally or through the germline (e. g. circoviruses, endogenous retroviruses etc.).

Moreover, it has been pointed out that adverse effects of microorganisms which are introduced into the recipient through xenografting may be indirect ones. for instance, patterns of antibiotic usage in animal husbandry differs from those in human medicine. Therefore, the introduction of bacteria from animal husbandry environments into human health care settings may introduce unanticipated patterns of antibiotic resistance, mandating vigilance (Chapman 2003).

- *Infection with unknown pathogens*. Several porcine viruses have only been detected recently, e. g. Nipah virus, circoviruses, γ herpes viruses, hepatitis E virus. Therefore, it is likely that more unknown viruses exist in the pig which might be transferred to humans through xenotransplantation and turn out to be pathogenic to humans.
- *Emergence of new pathogens*. It cannot be ruled out that new pathogens emerge after xenotransplantation. Several well-documented cases substantiate the fact that the pathogenic potential of a microorganism may change abruptly when the host environment changes. Examples are Hantavirus pulmonary syndrome[6] that results when a sin nombre virus is transmitted from an asymptomatic rodent into a human, or AIDS as a result of HIV infection of humans, while chimpanzees infected with the progenitor virus of HIV, SIV, are disease-free. Alternatively, the infectivity, pathogenicity and transmissiblitity of viruses may change in an unpredictable manner due to recombination between human and animal strains (Chapman 2003). Influenza is an example for this mechanism, but also endogenous retroviruses have the potential to develop into new pathogens, because they can cross the species barrier, can recombinate with other (defective) viruses, and can increase their virulence and host range through mutation and recombination.
- *Transmission of pathogens from xenograft recipients to the general population.* Cases are known in which pathogens (independent of xenotransplantation) crossed the species barrier to humans and were further transmitted among humans. This case cannot be ruled out for xenotransplantation. It has been pointed out that a given risk of infection may be acceptable for a xenograft recipient but not for the population (Bach et al. 1998; Stoye 1998). As a consequence, there was a call for a moratorium by the Parliamentary Assembly of the Council of Europe (Council of Europe et al. 1999).

Since the risk of infection inherent in xenotransplantation was recognized, there has been intensive research in order to broaden the data base and understanding for an assessment of this risk. Since the mid1990s, research has focussed on the group of porcine endogenous retroviruses (PERVs). However, in recent years other virus groups have also moved into the focus of research. (e. g. circoviruses, porcine encephalomyocarditis virus, swine hepatitis E virus, porcine herpesviruses, porcine cytomegalovirus) have also moved into the focus of research (Brewer et al. 2003; Brewer et al. 2004; Cheung 2004; Chmielewicz et al. 2003; Clark et al. 2003a; Crowther et al. 2003; Ehlers 2002; Fenaux et al. 2003; Gollackner et al.

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[6] Nearly half of all human cases of Hantavirus pulmonary syndrome are fatal.

2003; Mankertz 2002; Meng 2003; Mueller et al. 2002; Mueller et al. 2003; Rovira et al. 2002; Vincent et al. 2003).

Based on prerequisites which must be fulfilled so that porcine endogenous retroviruses can be considered to represent a risk for public health (Stoye 1998), de Wit 2001) has developed a model of progressive public health risk due to xenozoonoses irrespective of the infectious agent that causes the health risk (table 4.2). However, no consensus has been reached up to now at which stage of this model a given pathogen will rule out xenotransplantation (de Wit 2001).

Table 4.2: Model of progressive public health risk due to xenozoonoses

Stage	Public health risk
1. Infectious agents must exist in pigs	
2. Infectious agents must exist in source animals	
3. Infectious agents must be present in organs	
4. Infectious agents are released after xenotransplantation	
5. Infectious agents must infect recipient	
6. Infectious agents must multiply and spread in recipient	
7. Infectious agents must cause a disease in humans	
8. Infectious agents must be transmitted from man to man	

Source: Adapted from de Wit 2001; Stoye 1998

In the following paragraphs and in table 4.3, the present knowledge regarding porcine endogenous retroviruses is summarized. Recently, reviews on our knowledge on PERVs have also been published (Blusch et al. 2002a; Chapman 2003; Magre et al. 2003; Patience et al. 2002).

Table 4.3: Overview of present knowlegde regarding health risks arising from PERV infections

Stage	Example PERV	Source
1. Infectious agents must exist in pigs	yes, widely distributed	Akiyoshi et al. 1998; Le Tissier et al. 1997; Martin et al. 1998; Oldmixon et al. 2002
2. Infectious agents must exist in source animals	yes, many genomic copies	
3. Infectious agents must be present in organs	yes, all relevant organs	Le Tissier et al. 1997; Martin et al. 1998; Onions et al. 1998; van der Laan et al. 2000; Wilson et al. 1998
4. Infectious agents are released after xenotransplantation	???, vage evidence from SCID mouse	van der Laan et al. 2000
5. Infectious agents must infect recipient	???, in vitro yes, no evidence for in vivo infection in humans	in vitro: Patience et al. 1997 in vivo: see table 4.4 non-human primates: Ritzhaupt et al. 2002.
6. Infectious agents must multiply and spread in recipient	???, vage evidence from SCID mouse	van der Laan et al. 2000
7. Infectious agents must cause a disease in humans	not known, only analogy to other retroviruses	Allan 2003; Denner 1998, 1999; Tacke et al. 2000
8. Infectious agents must be transmitted from man to man	not known	

Porcine endogenous retroviruses (PERVs) are present in the genomes of various pig races. In races which are also used as source animals for xenotransplantation up to fifty copies of PERVs have been detected (Akiyoshi et al. 1998; Edamura et al. 2004; Le Tissier et al. 1997; Lee et al. 2002; Martin et al. 1998; Zhang et al. 2003). Research is underway to identify those PERV copies which are intact, defective or infectious, respectively (Bartosch et al. 2002; Bösch et al. 2000; Gorbovitskaia et al. 2003; Herring et al. 2001b; Niebert et al. 2002; Niebert et al. 2003a; Niebert et al. 2003b; Quinn et al. 2004). As no PERV is present in every pig, it seems feasible that a genetic selection can be designed to identify animals lacking a potentially active PERV at a specific locus so that pigs could be generated by conventional breeding free of certain functional PERV. While it does not seem possible to remove all fifty copies from the genome using conventional breeding or gene knock-out technology (Stoye 1998), this might be technically feasible for a limited number of copies. The gene knock-out technology has become available for pigs in 2001 (see chapter 4.5). Moreover, lines of inbred miniature swine have been identified which do not produce PERV particles capable of infecting human cells in vitro (Oldmixon et al. 2002; Scobie et al. 2004; Wood et al. 2004).

Three classes of these PERVs are known which differ primarily in their envelope genes, use different receptors (Ericsson et al. 2003; Tönjes 1999) and therefore differ also their host range (Takeuchi et al. 1998; Wilson et al. 2000). In recent years, intensive efforts have been undertaken in the molecular characterisation of PERV sequences and gene products (see e. g. Avidan et al. 2003; Blusch et al. 2002b; Hazama et al. 2003; Klymiuk et al. 2002, 2003; Ramachandran et al. 2003a; Ramachandran et al. 2003b; Scheef et al. 2002; Scheef et al. 2001; Suling et al. 2003; Tonjes et al. 2003; Wilson et al. 2003).

These retroviral sequences are expressed in vitro in a large variety of porcine cell types and tissues (e. g. spleen, heart, kidney, endothelic cells, liver cells, skin, lung, pancreatic islet cells, bone marrow cells and certain blood cells) and therefore also in the organs and tissues which would be transplanted in clinical xenotransplantation (Le Tissier et al. 1997; Martin et al. 1998; McIntyre et al. 2003; Onions et al. 1998; van der Laan et al. 2000; Wilson et al. 1998). These PERVs can infect human cells (Czauderna et al. 2000; Kuddus et al. 2003; Patience 2001; Patience et al. 1997; Specke et al. 2001a) and also cells of many other species (Specke et al. 2001b) in vitro. After passaging on human cells, adaption of the viruses by genetic alterations in long terminal repeats was observed which led to higher virus titers (Denner et al. 2003). Similar genetic alterations are associated with enhanced tumorigenicity in other gamma retroviruses (Denner et al. 2001a). These long terminal repeats are characterised further (Wilson et al. 2003). At present, it is not known whether PERVs could cause diseases in humans, but in general, most retroviruses can cause tumors or immunodeficiencies (Denner 1998, 1999; Tacke et al. 2000).

However, there is no conclusive evidence whether transfer of PERVs to other animal and human cells does not only occur in vitro, but also in vivo. Table 4.3 gives an overview of publications in which patients who had had contacts with pig products in a way that they might have been infected by PERVs (e. g. receiving xenogenic transplants, treatment by extracorporal perfusion of porcine organs or tissues, blood-blood contact with PERV contaminated material) were examined for signs of infection with PERVs. A discussion of these data can also be found in Herring et al. 2001a. In none of these cases, conclusive evidence for an infection with PERVs could be obtained. Although some of the data suffer from methodological limitations (see in-depth discussion in Hüsing et al. 2001; Hüsing et al. 2000; Specke et al. 2003), the overall information obtained so far supports the notion that PERVs are not highly infectious viruses and that infection of humans with PERVs is likely to be a rare event.

In vivo infection with PERVs has been observed in a SCID mouse model which received porcine islet cells (van der Laan et al. 2000), but cannot be anambigiously distinguished from microchimerism. Other models are being established to test whether PERV transmission from porcine tissue to other species can occur in more in-vivo like settings than in cell cultures (Clemenceau et al. 2002). It is also investigated whether human cells can fuse in

vivo with cells of disparate species (e. g. pig) because this could be another mechanism of transspecies pathogen transmission (Ogle et al. 2004).

At present, research is underway to establish small animal models or non-human primate models in which in vivo transmission of PERVs could be studied. Up to now, PERV infection followed by replication has not been detected in small animal models and non-human primates which received PERVs or porcine cells or organs, even during severe immunosuppression (Argaw et al. 2004; Denner et al. 2001b; Edamura et al. 2004; Loss et al. 2001; Martin et al. 2002; Specke et al. 2002a; Specke et al. 2002b; Specke et al. 2001b). This points to the difficulty of finding suitable models to study possible PERV transmissions to humans because cells from non-human animals can only be infected, but no productive replication of the viruses takes place.

That PERVs may be of concern due to the possible risk of infection is no longer limited to the field of xenotransplantation. Porcine tissues, both living and decellularised, are also used in tissue engineering (Bock et al. 2003; Hüsing et al. 2003a). Therefore, it has been investigated whether there is a risk of transmitting PERVs with tissue engineered products (Kallenbach et al. 2004; Leyh et al. 2003; Petersen et al. 2002; Walles et al. 2003). No transmission of porcine endogenous retrovirus could be detected.

These data show that PERVs are not highly infectious viruses, but many questions still remain unanswered, among them

- Are PERVs expressed and produced after xenotransplantation in humans?
- Under which conditions (e. g. cell-cell contact, immunosuppression, virus adaptation) can the release of infectious PERV particles take place, perhaps even longer times after transplantation?
- Which influence do genetic modifications of the source animals have on the likelihood of infectivity with and adaptation of PERVs (Kurihara et al. 2003; Takefman et al. 2002; Weiss 1998)?
- Are there differences between different organs? Are certain human cell types or tissues more susceptible to PERV infection than others?
- Are PERVs pathogenic to humans? Can they be transmitted from human to human?

Table 4.4: Overview of published analysis of human beings with blood contact to porcine tissues for signs of PERV infection

Therapy	Number of tested persons	Result	Source
Extracorporal perfusion of pig kidney	2	no evidence of PERV infection detected by the applied analytical methods	Paradis et al. 1999; Patience et al. 1998a
Xenotransplantation of porcine islet cells	14		10 of these patients: Heneine et al. 1998; 14 patients: Paradis et al. 1999 (8 patienten were examined twice)
Xenotransplantation of alginate encapsulated porcine islet cells, one recipient immunosuppressed	2		Elliott et al. 2000
Extracorporal perfusion of pig liver	1		Paradis et al. 1999
Extracorporal perfusion of spleen from slaughterhouse pigs during immunotherapy	100		Paradis et al. 1999
Xenotransplantation of porcine skin for treatment of severe burns	15		Paradis et al. 1999
Xenotransplantation of fetal porcine neuronal cells for therapy of Parkinson's disease, Huntington's disease and epilepsy	24		Dinsmore et al. 2000; Schumacher et al. 2000
Extracorporal perfusion of a bioartificial liver assist device (HepatAssist) incorporating porcine liver cells	28		Paradis et al. 1999; Pitkin et al. 1999
Extracorporal perfusion of a bioartificial liver assist device incorporating porcine liver cells	5		Kuddus et al. 2001; Kuddus et al. 2002
Extracorporal perfusion of a bioartificial liver assist device incorporating primary liver cells from specific pathogen-free pigs	1		van_de_Kerkhove et al. 2003

Extracorporal perfusion of a bioartificial liver assist device incorporating primary liver cells from specific pathogen-free pigs	8 7		Irgang et al. 2003; Sauer et al. 2003
Extracorporal perfusion of transgenic pig livers (hCD55/hCD59)	2		Levy et al. 2000; Xu et al. 2003
Treatment of treat severe bleeding episodes in persons with hemophilia who have antibodies to human clotting factor with unheated porcine clotting factor VIII (Hyate:C)	88 (+ 23 non-exposed controls)		Heneine et al. 2001
Healthy blood donors Pregnant women	569 38		Tacke et al. 2001
Butchers directly and daily engaged in pig slaughter Butchers routinely handling raw pig meat	14 30		Tacke et al. 2001

Although the knowledge of PERVs has been considerably enlarged since their risk potential in xenotransplantation was recognised in the mid 1990s, the risk of infection by known or unknown viruses cannot totally be excluded. Moreover, preclinical research is approaching its limits, and the risk of infection could only be further elucidated if porcine organs were transplanted into human beings (Patience et al. 1998b; Stoye 1998).

Therefore, measures for the prevention and control of events of infection are required. They comprise (Boneva et al. 2001; Onions et al. 2000)

- the breeding and housing of specific pathogen free source animals,
- the development of highly sensitive and specific detection methods for the infectious agents,
- the implementation of monitoring measures which aim at early detection of any infection events and prevention of transmission,
- the development of drugs for the control of the infectious agents, or the development of vaccines.

Recommendations which infectious agents should be excluded from source animal herds have been developed (Muir et al. 2001), have been evaluated in practice and recommendations for improvement have been obtained (Tucker et al. 2002; Tucker et al. 2004).

Highly sensitive and specific detection methods for PERVs have been developed (e. g. Argaw et al. 2002; Blusch et al. 2000; Fischer et al. 2003; Niebert et al. 2003b; Seifarth et al. 2003; Shah et al. 2003; Tacke et al. 2001) and used in monitoring and detection of infection events (see also table 4.4). In addition to PERVs, other virus groups have also moved into the focus of research in recent years (e. g. circoviruses, porcine encephalomyocarditis virus, swine hepatitis E virus, porcine herpesviruses, porcine cytomegalovirus) (Brewer et al. 2003; Brewer et al. 2004; Cheung 2004; Chmielewicz et al. 2003; Clark et al. 2003a; Crowther et al. 2003; Ehlers 2002; Fenaux et al. 2003; Gollackner et al. 2003; Mankertz 2002; Meng 2003; Mueller et al. 2002; Mueller et al. 2003; Rovira et al. 2002; Vincent et al. 2003), so that research is underway to develop comparable methods also for other porcine viruses.

Requirements for monitoring measures have been discussed also on supranational and national level (OECD 2001; United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) 1998, 1999a, b; World Health Organization (WHO) 1998). Regulations are being implemented on supranational level (see table 5.1). At least for therapeutic applications of cellular xenotransplantations, a legally binding framework has been established: xenogeneic cell therapy has been included into the EU Directive on medicinal products (Commission Directive 2003/63/EC of 25 June 2003 amending Directive

2001/83/EC relating to medicinal products for human use), so that regulatory oversight is formally established and an authorisation according to medicinal products will be required prior to clinical use. In order to establish guidance how this evaluation and authorisation should be performed, the European Agency for the Evaluation of Medicinal Products (EMEA) has recently adopted points to consider on xenogeneic cell therapy medicinal products (EMEA et al. 2003), after a concept paper on the development of points to consider on xenogeneic cell therapy had been issued in 2000 (EMEA 2000). The points to consider take into account requirements for sourcing of animals, manufacturing of the xenogeneic cells, non-clinical testing, proof of human efficacy and safety, as well as pharmacovigilance and special surveillance methods.

Several options of managing PERV infections once they should have occurred have been further explored: A screening for drugs which could inhibit PERV replication has been carried out (Qari et al. 2001; Wilhelm et al. 2002). Vaccines against related gamma retroviruses, such as feline leukemia virus, have been developed. Therefore, it is not unlikely that vaccines against PERVs could also be developed (Gesellschaft für Virologie e. V. et al. 2002). Research is underway to explore the possibility of an anti-PERV vaccine or antiserum further (Dekker et al. 2003; Fiebig et al. 2003). However, there are doubts whether vaccines can be of use in immunosuppressed patients (de Wit 2001).

4.4 Physiological compatibility of xenograft and recipient

The question to which extent a xenograft will function successfully in the foreign milieu of the xenograft recipient has been relatively neglected in xenotransplantation research. Therefore, a relatively small amount of information is available on this issue. Immunological and microbiological problems have received much more intensive investigation. This situation is due to the fact that the poor survival rates achieved in xenotransplantation studies to date have not permitted a thorough analysis of the physiological function of a xenograft in the long term. Despite the limited knowledge, several physiological incompatibilities have already been encountered, and others will still remain to be discovered, so that physiology most likely constitutes a significant stumbling block to the progress of xenotransplantation towards clinical trials (Dobson et al. 2002).

The state of knowledge regarding the physiology of xenotransplantation of porcine organs has been reviewed by de Wit 2001 and also by Dobson et al. 2002) in September 2002 on behalf of the British Department of Health in order to primarily assist the British Xenotransplantation Interim Regulatory Authority (UKXIRA) in its regulatory role, but also to inform the interested public about it. The following questions were analysed:

- *Anatomy*. Regarding anatomical compatibility of porcine and human organs, the organ size, organ structure and the surgical techniques to transplant the organs must be taken into consideration.
- *Nutrient supply*. This aspect primarily relates to blood and blood circulation and whether the porcine organs will be adequately supplied with nutrients so that any damage due to over- or undersupply can be prevented.
- *Molecular incompatibilities*. Several physiological functions and regulatory mechanisms may be impaired due to molecular incompatibilities among the species.

Both reviews came to the conclusion that the assessment of physiological (in)compatibility is organ-specific. Regarding anatomy, only few data are available on the anatomy of porcine hearts, and even less on the anatomy of other porcine organs. Major differences exist which are mainly due to the up-right position of the two-legged human body versus the supine position in the four-legged pig. Their relevance for the clinical setting is difficult to assess. The development of appropriate surgical procedures does not pose a major problem, but it cannot be ruled out that the fitness and performance of porcine organs in the human host will be impaired due to anatomical reasons.

A sufficient blood flow is a prerequisite for appropriate organ function in order to supply it with oxygen and nutrients and to remove metabolic degradation products. There are many differences between human and porcine blood, e. g. in haemoglobin content, haematocrit, blood viscosity and red blood cell diameter. These differences could lead to disturbed haemoperfusion and inadequate function of donor organs in the human recipient. Furthermore, the process of coagulation involves many different factors, some of which are known to be species-specific (e. g. thrombomodulin, tissue factor pathway inhibitor and von Willebrandt Factor). Coagulation disturbances have already been reported from several pig to non-human primate xenotransplantation models. Moreover, reduced haemoperfusion of xenogeneic organs has also been observed by many groups and attributed largely to the presence of leukocytes and thrombocytes in the microcirculation. Crucial differences in the composition and viscosity of porcine and human blood suggest that the microperfusion of organs will be severely compromised leading to reduced blood flow, blood stasis and thrombosis, even in the absence of rejection. According to Dobson et al. 2002 these differences in blood properties will present major problems for the future of xenotransplantation.

Many molecular differences are already known regarding human and porcine enzymes, hormones, and lipoproteins, and it is likely that they will also represent major hurdles for clinical xenotransplantation (Hammer 2002; Hammer 2003). However, at present their clinical relevance is difficult to assess: it is not known which or how many of these differences will significantly impair the xenoorgan function, and whether certain

incompatibilities can be overcome by medication or genetic engineering of the source animal.

According to today's knowledge, the xenotransplantation of porcine **hearts** appears to be the least susceptible to major physiological incompatibility problems (de Wit 2001; Ogata et al. 2004; Pham et al. 2004). Although survival times with life-supporting xenografts of appr. one month have been achieved in the pig-to-non-human primate model (see table 4.1), the onset of lethal disrhythmias in some experimental animals suggests that anatomical differences in the intrinsic innervation of the heart may be a major factor in morbidity rates in longer-term survivors (Dobson et al. 2002), so that long-term monitoring (and control) of blood pressure and pumping performance may be required.

Some of the longest survival rates of life-supporting xenografts to date have been achieved for the xenotransplantation of **kidneys** (up to 78 days, see table 4.1). Some physiological parameters (water and acid-base) have been maintained within normal limits for up to 30 days after transplantation. One molecular incompatibility problem is known: porcine erythropoietin does not function in the non-human primate host. However, the formation of anaemia could be prevented by substituting the non-human primates with recombinant human erythropoietin. However, differences in the renal handling of creatinine, urea, and electrolytes such as calcium and phosphate have been observed which require further research in long-term experiments.

The **liver** is an extremely complex organ and the numerous enzymes, hormones and regulatory pathways depend on species-specific interactions. Therefore, liver xenotransplantation presents far more potential for physiological incompatibilities than cardiac or renal xenotransplantation. Major differences are apparent in, to name but a few, in the structure and serum concentration of important transport proteins such as serum albumin – severe hypoalbuminaemia in a xenograft recipient would be lethal. Levels of platelets, phosphate, creatinine and total bilirubin are also much higher in pigs than in humans, so that this will most likely cause severe problems.

The xenotransplantation of **lungs** seems to be the least advanced of all solid organs (Cantu et al. 2004). Only few experiments have been carried out to date, and the xenograft recipients remained unconscious and in the supine position throughout the experiment. The extremely low survival rates have permitted little interpretation of the physiological data. The effects of postural changes on lung function have not been determined. However, increased resistance in the small pulmonary vessels of the porcine lung compared to the baboon lung suggests that lung function may be compromised in a xenotransplant recipient.

Although the database regarding physiological compatibility is far from complete and comprehensive, major problems are foreseeable, which however differ for the different organs. At present, medical intervention and genetic engineering of the source animal have

been suggested as options to overcome incompatibilities (Platt 1998a; Platt 1998b). However, given the numerous incompatibilities which must possibly be targeted, these strategies may not be feasible.

4.5 Genetic engineering of source animals

Animals are used in xenotransplantation in different roles and with different consequences for the animal. Table 4.5 gives an overview of these roles and consequences.

Table 4.5: Different roles of animals in xenotransplantation, and the corresponding consequences for the animal

Problem	Role of the animal	Consequences for the animal
Lack of sufficient numbers of human donor organs	Life saver Improver of quality of life	Death of source animal, since source animals will be killed after explantation of the graft
Rejection of xenografts	Foreign body	Humanizing by genetic engineering/cloning
Risk of pathogen transmission from source animal to human recipient	Pathogen source	pathogen-free by raising under SPF conditions, breeding, genetic engineering/ cloning
Early stage of R&D, lack of knowledge and understanding of processes underlying XTP, need to prove quality, safety, efficacy of XTP	Model for man in preclinical research	Surgery, medication, infection, death

At present, the common opinion in the xenotransplantation community is: pigs, but not non-human primates should be used as source animals; non-human primates may be used in preclinical research as model for man (as xenograft recipient, in infection studies).

The techniques of genetic engineering and cloning play a major role in xenotransplantation research, because altering the genetic make-up of the source animals is seen as a major strategy to overcome problems of xenotransplantation in the fields of rejection, risk of infection, and physiological compatibility (Yang et al. 2000).

In 1995, the first transgenic pigs became available which expressed human complement regulatory proteins (Cozzi et al. 1997). This genetic modification made it possible to overcome hyperacute rejection and genetic modification was achieved by the technique of microinjection. It is, however, unlikely that transgenic pigs can be produced by microinjection

which harbour more than three foreign genes (such animals had been produced by 1998; see e. g. Costa et al. 2002; Cowan 2000). Therefore, the available techniques for the genetic modification of pigs presented a major bottleneck for xenotransplantation research when it became evident that additional modifications in the genetic make-up of the source animals would be required for successful xenotransplantation.

Since 1995, major breakthroughs have been achieved in expanding the methodological toolbox for the genetic modification of pigs (Nagashima et al. 2003b; Niemann et al. 2001a; Piedrahita et al. 2004; Prather et al. 2003; Wheeler et al. 2001). In 2000, the cloning of pigs by nuclear transfer of adult or fetal cells was reported (Betthauser et al. 2000; Onishi et al. 2000; Polejaeva et al. 2000), and also transgenic pigs were produced using this method. The availability of this method made it possible for the first time not only to add foreign genes to the pig genome, but also to knock out certain genes. The knock-out technique is thought to be of major use in creating pigs devoid of the epitope which triggers hyperacute rejection and devoid of infectious PERV sequences.

In late 2001, two competing groups succeeded in producing the first knock-out pigs. These pigs were devoid of one copy of the α-1,3-galactosyltransferase gene (Dai et al. 2002; Lai et al. 2002). However, both copies of this gene must be inactivated in order to achieve the desired properties, but it was not known whether pigs devoid of both copies would be viable (Butler 2002; Frankish 2002; Kaiser 2002). Meanwhile, both groups have also produced the first double knock-out pigs which were born in August 2002 (Phelps et al. 2002; PPL Therapeutics 2002) and November 2002 (BioTransplant Incorporated 2003). They seem to be healthy. The next step is to investigate whether organs from these pigs are effective in preventing hyperacute rejection. First data from BioTransplant Inc. and Immerge BioTherapeutics were presented at the American Transplant Congress in Washington, June 2003, showing over two-month survival of a life-supporting kidney graft and a heart graft[7]. At present, the aim is to combine multiple genetic modifications in pigs which do not transmit PERVs to human cell lines and which are double knock-outs for the α-1,3-galactosyltransferase gene. Given the time for reproduction of pigs, this aim might be technically achievable by 2005. However, both BioTransplant Inc. and PPL Therapeutics are in severe financial problems and seem to have terminated their activities in the field of xenotransplantation R&D. At present (spring 2004) it is not yet clear whether and in which organisational settings these R&D activities will be continued.

In addition, there has been substantial progress in the knowledge how PERVs are distributed in the pig genome and what their prevalence in different pig races is. Although up to fifty copies of PERVs can be found in the pig genome, no PERV is present in every pig. Therefore, it seems feasible that a genetic selection can be designed to identify animals

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[7] http://www.immergebt.com/our_research/index.php, accessed April 21, 2004

lacking a potentially active PERV at a specific locus so that pigs could be generated by conventional breeding free of certain functional PERV. In addition, a limited number of PERV genes could be eliminated by the knock-out technology (see above). Some inbred miniature swine have been identified which fail to produce human-tropic replication-competent porcine endogenous retrovirus, using in vitro coculture assays (Oldmixon et al. 2002; Scobie et al. 2004; Wood et al. 2004). Thus, he risk of infection with PERVs could be further reduced when pigs such as this line of miniature pigs were used for further genetic modification of source animals.

The production of source animals for xenotransplantation and the use of animals in preclinical XTP research is a significant utilization of animals solely for human purposes. Essential prerequisites for this utilization is the application of reproductive technologies (such as superovulation, artificial insemination, embryo transfer etc.), genetic modification of animals, and reproductive cloning of animals. These techniques can significantly impair health, well-being and behaviour of the animals involved. From both an ethical and an animal welfare perspective it must be asked to which extent these impairments of the involved animals can be justified by the goals of XTP, and whether these goals could also be reached by other, more acceptable means. In the following paragraphs, the impacts of the technologies applied to XTP source and research animals are outlined.

Livestock reproductive technologies can have impacts on the health and well-being of the parent animals, of the surrogate mothers as well as the offspring. Female parent animals are treated with hormones in order to affect fertility, to alter ovulation cycles and to achieve superovulation; surrogate mothers are also prepared by hormone treatments in order to successfully take up transferred embryos. In order to obtain oocytes or embryos for in-vitro procedures (e. g. genetic modification, somatic cloning), surgical procedures have to be performed on the mother animal. The efficiency of reproductive technology procedures is much lower than their "natural" counterpart processes. As a consequence, reproductive technologies require an excess of animals, germ cells and embryos. Abnormalities seem to be more frequent in offspring derived from reproductive technologies than from "natural" breeding (Brink et al. 2000; Bulfield 2000; Long et al. 2003; Tatham et al. 1998; Thibier et al. 2002; van Arendonk et al. 2002; Vishwanath 2003).

The following problems are related to genetic modification of animals (Bichard 2002; Bondioli et al. 1998; Brink et al. 2000; Bulfield 2000; Clark et al. 2003b; DePalma 2003; Houdebine 2002; Kleter et al. 2002; Larrick et al. 2001; Nagashima et al. 2003a; Pew Initiative on Food and Biotechnology 2004; Powell 2003; Prather et al. 2003; Rudolph 1999; Wall 2002; Ward 2000):

- *Inefficient methods of gene transfer.* Due to the low efficiency of the reproductive and gene transfer methods, large numbers of oocytes, female animals as oocyte donors and

embryo recipients, as well embryos being subjected to genetic modification procedures are required. Embryos subjected to genetic modification procedures are often impaired in their development so that there is a relatively high number of miscarriages.

- *Unintended impacts due to position effects of the inserted gene.* The site at which the foreign gene integrates into the genome cannot be precisely targeted with the presently available gene transfer methods. The recipient animal can therefore be negatively be affected if the introduced gene inserts into functional genes, thus interrupting them and rendering them unfunctional or functionally impaired. In addition, the expression of the newly introduced gene can also be negatively affected due to the surrounding genome structure into which it was inserted.
- *Unintended impacts due to expression of the inserted gene.* Especially if the inserted genes code for gene products with high biological activity, the wellbeing and health of the genetically modified animal could be negatively affected by the genetic modification. For example in XTP, it was not known whether double knock-out pigs for the a-1,3-xxx transferase would be viable or whether this gene locus fulfilled an essential function in pigs.
- *Impacts of animal housing conditions, depending on the intended use of the genetically modified animal.* In order to reduce the risk of infection, source animals for XTP must be raised under specific housing conditions which do not comply with the animals' needs.

Since Dolly the sheep has been cloned in 1997, substantial evidence has been collected on the adverse effects of this technique to the cloned animal. While first reviews of the health profile of cloned animals stated that they "seemed to be normal" (Cibelli et al. 2002; Lanza et al. 2001), more recent reviews stress the high inefficiency of the method due to several developmental aberrancies, such as a high rate of abortion during early gestation, "large offspring syndrome", increased perinatal death (Han et al. 2003) and more subtle phenotypic abnormalities that can only be revealed by detailed pathological studies (Rhind et al. 2003a; Rhind et al. 2003b). Evidence emerges that defects of cloned embryos may be due to inclomplete epigenetic reprogramming of donor genomic DNA (Fulka et al. 2004; Han et al. 2003; Wilmut et al. 2002). This results in major dysregulation of gene expression, particularly in the placenta, with long-lasting effects into adulthood in some surviving clones.

Against this background, it has been suggested to favour embryonic cloning over somatic cloning for livestock production and modification; this, however, would require the isolation of livestock embryonic stem cells which has – despite intensive efforts - not yet been achieved (Wells et al. 2003).

4.6 Clinical experience with xenotransplantation

4.6.1 Non-human primates as xenograft recipients

Presently, several hundred (at least more than 400) non-human primates have been transplanted with organs from transgenic pigs in the course of preclinical xenotransplantation research. Selected experiments which yielded the longest survival times are listed in table 4.1 and commented in chapter 4.2.

4.6.2 Humans as xenograft recipients

4.6.2.1 Overview of recent xenotransplantation procedures with humans as recipients

Until today, more than 300 patients worldwide have been treated with porcine cells, tissues and organs. The majority of patients has been treated with some sort of cellular xenotransplantation, and only very few with organ xenotransplantation. Most of these xenotransplantations took place in clincial trials for the treatment of Parkinson's disease using fetal porcine neural cells, in clinical trials for the treatment of acute hepatic failure, using extracorporal liver assist devices with porcine liver cells, and in trials for the treatment of diabetes, using porcine islet cells. However, in these trials hardly any therapeutic effect which could be attributed to the action of the transplanted cells could be observed (Hüsing et al. 2001).

Regarding organ xenotransplantation, a general consensus has emerged in the last years that the individual and collective risks at present are not outweighed by the possible benefit so that no organ xenotransplantation should be performed at present. The International Society of Heart and Lung Transplantation has published a position paper on the present status of xenotransplantation and its potential role in the treatment of end-stage cardiac and pulmonary diseases. They give detailed and precise recommendations which conditions must be fulfilled before clinical trials may be started (Cooper et al. 2000a):

- Current experimental results indicate that a clinical trial of heart xenotransplantation at present is premature, and that experimental lung xenotransplantation is in an extremely primitive stage of development and clinical trial cannot be considered at the present time,
- A xenotransplantation 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,
- 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 xenotransplantation procedures for the foreseeable future,

- A xenotransplantation 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. These goals should be achieved in the absence of life-threatening complications from the immunosuppressive regimen.
- 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.

Although these recommendations only relate to the xenotransplantation of heart and lung, and there are differences in the state of the art between different organs (see chapter 4.4), the recommendation that clinical xenotransplantation trials should only be done within an internationally accepted regulatory framework and under supervision of a nationally or internationally recognised regulatory body holds true for all applications of xenotransplantation. As McKenzie et al. 2002 point out, non-compliance with these recommendations will prove harmful to the development of xenotransplantation as a treatment.

Against this background, one should not expect any recent organ xenotransplantations involving humans as transplant recipients being carried out in the last years. However, media reports suggest that at least a few clinical organ xenotransplantations have been performed. This raises doubts whether these procedures were totally in line with the above mentioned recommendations. The cases that became known are

- a combined transplantation of a porcine kidney, a porcine heart and a porcine lung in India in 1997 (Jayaraman 1997; Sharma 1999),
- an extracorporal perfusion with unmodified pig livers of a patient suffering from acute hepatic failure in Germany in 1999 (Koch 1999; sago 1999), and
- two cases of extracorporal perfusions with pig livers from genetically modified source animals in the USA, bridging two patients with acute hepatic failure to liver allotransplantation (Levy et al. 2000).

Clinical application of cellular xenotransplantation is not totally excluded at present because the risk-benefit assessment may come to more favourable results than for organ

xenotransplantation (Hüsing et al. 2001). Nevertheless, concern has been expressed on clinical trials for the treatment of diabetes in which porcine islet cells are transplanted into diabetes patients because they are performed in Mexico, and may be expanded in cooperation with the New Zealand based company Diatranz to the Cook Islands (Anonymous 2002; Archer et al. 2002; Collignon 2002; Dalton 2002; McKenzie et al. 2002; Valdes Gonzalez 2002; Valdes 2002).

4.6.2.2 Time scale of clinical realisation of xenotransplantation

At present, it is highly uncertain whether and when the xenotransplantation of organs will reach the stage of clinical applications. It is most likely, that knowledge will be accumulated starting with cellular xenotransplantation, then using xenogeneic organs as organ assist devices in extracorporal perfusions (e. g. liver, kidney), and then as bridges to allotransplantation. Table 4.6 gives an overview of the possible time scale of development.

Table 4.6: Possible time scale of clinical realisation of xenotransplantation

Type of xenotransplantation procedure	Possible time scale
Cellular xenotransplantation (liver assist device, Parkinson, diabetes)	Clinical trials ongoing
Extracorporal perfusion (transgenic livers and kidneys)	2 single cases in 2000 (USA) 1-5 years from now?
Xenograft as bridge to allograft	2-5 years from now?
1-year survival of xenograft	5-10 years?
Clinical routine	15-20 years?

Whether this possible time scale is realistic, does not only depend on whether the required scientific breakthroughs can really be achieved. It also depends on the implementation of international regulation of xenotransplantation, on financial resources allocated to this sector (during the last years and still ongoing, there is an intensive restructuring process of xenotransplantation companies which is most likely due to financial problems), on financial resources available for organ transplantation in the national health care systems, and on the development of possible alternatives to xenotransplantation (e. g. within regenerative medicine the use of human stem cells instead of cellular xenotransplantation) (Hüsing et al. 2003b).

4.6.2.3 Impacts on the patient's survival and quality of life

In view of the many questions which are still open regarding xenograft rejection, physiological compatibility, and risk of infection, it is most likely that for at least a decade or even more the function and longevity of xenografts in the human recipient will be inferior to the performance of allografts (Hüsing et al. 2000). These disadvantages must be balanced against the possibly better availability of the xenograft.

4.6.2.4 Impacts on the patient's identity, personality and emotions

There is concern that the transplantation of xenogeneic cells, tissues or organs could have negative impacts on the patient's identity, personality and emotions. This concern is often explained by the known phenomenon of microchimerism: in allotransplantation as well as xenotransplantation donor cells can migrate in the recipients body, so that they do not stay totally confined to the initial transplantation site. However, surgeons and xenotransplantation scientists do not see a causal relationship between microchimerism and possible impacts on xenograft recipients' identity and personality.

Relevant questions regarding patient's identity, personality and emotions comprise (Kirchenamt der Evangelischen Kirche in Deutschland et al. 1998):

- Will a patient suffer from emotional stress due to the knowledge that the transplant is of porcine origin?
- Will this patient develop a feeling of inferiority towards other human beings or towards recipients of a human allograft?
- Which impact has the transplantation of a xenogeneic organ on the identity of a diseased person?
- Will other people observe the xenograft recipient in his emotions and behaviour?
- How can a positive attitude towards life with the foreign animal organ be developed, how can the foreign animal organ be accepted as a equally good substitute for one's own diseased organ and as constitutent of one's body, if significant comforting elements of allotransplantation (e. g. free will of donation, organ as a present) are not present in xenotransplantation?

Some of these questions have been addressed in surveys regarding attitudes towards xenotransplantation. However, it is not known how answers and preferences in these surveys would correspond to actual behaviour once xenotransplantations would be performed clinically. From allotransplantation, it is known that patients differ in their ability to cope with the transplantation of an organ psychologically, and that these differences in ease of coping are correlated with their type of "concept of one's own body" (Schröder et al. 2001).

Table 4.7: Clinical experience with humans as xenograft recipients

Disease	Type of cell/tissue/organ	Patients treated/planned	Country	Clinical trial phase	Results	Year	Study pursued further
Heart failure	chimpanzee heart	1			death of patient after 2 h	1964	no
Heart failure	sheep heart	1			immediate death of patient	1968	no
Heart failure	pig heart	1			immediate death of patient	1968	
Heart failure	chimpanzee heart	1			death of patient after 4 h	1969	no
Heart failure	chimpanzee heart	1	South Africa		death of patient after 4 days	1977	no
Heart failure	baboon heart	1	South Africa		death of patient after 5 h	1977	
Heart failure	baboon heart	1	USA		death of patient after 20 days	1984	
Heart failure	pig heart	1			death of patient after 1 day	1992	
Kidney failure	chimpanzee kidney	12	USA		Patients survival up to 9 months	1964	
Kidney failure	baboon kidney	1			patient survival 5 days	1964	
Kidney failure	baboon kidney	6			patient survival up to 60 days	1964	
Kidney failure	chimpanzee kidney	1			patient survival 1 day	1964	
Kidney failure	chimpanzee kidney	3			patient survival up to 49 days	1964	
Kidney failure	chimpanzee kidney	2			patient survival 4 months	1965	
Kidney failure	chimpanzee kidney	1			patient survival 31 days	1966	
Multiorgan failure	transplantation of pig heart, kidney, lung	1	India	-	death of patient	1997	no
Hepatic failure	chimpanzee liver	1	USA		patient survival < 1 day	1966	
Hepatic failure	chimpanzee liver	1	USA		patient survival 9 days	1969	
Hepatic failure	chimpanzee liver	1	USA		patient survival < 2 days	1969	
Hepatic failure	baboon liver	1			patient survival < 1 day	1969	
Hepatic failure	baboon liver	1			patient survival 3 days	1970	
Hepatic failure	baboon liver	1			patient survival < 1 day	1970	

Table 4.7 continued

Disease	Type of cell/tissue/organ	Patients treated/planned	Country	Clinical trial phase	Results	Year	Study pursued further
Hepatic failure	baboon liver	1			patient survival < 1 day	1971	
Hepatic failure	baboon liver	1			patient survival 3 days	1971	
Hepatic failure	chimpanzee liver	1		USA	patient survival 14 days	1974	
Hepatic failure	baboon liver	1		USA	patient survival 70 days	1992	
Hepatic failure	baboon liver	1		USA	patient survival 26 days	1993	
Hepatic failure	pig liver	1			patient survival < 2 days	1993	
Hepatic failure	pig liver (extracorporal perfusion)	1	DE	-	death of patient	1999	no
Hepatic failure	Hepatoblastoma cell line (extracorporal perfusion) ELAD	23	UK	Phase 1		2000	yes
Hepatic failure	primary pig hepatocytes (extracorporal perfusion) BELS	8	D	Phase 1	successful bridging to allotransplantation	2000	no
Hepatic failure	transgenic pig liver (extracorporal perfusion)	2	USA	?	successful bridging to allotransplantation	2000	?
Hepatic failure	primary pig hepatocytes (extracorporal perfusion)	0/6	USA	Phase 1 approved	not yet available	2001	?
Hepatic failure	primary pig hepatocytes (extracorporal perfusion) BAL	39/39 ?/140	USA, B, D, I, NL, ES	Phase 1/ 2 Phase 2/ 3	well tolerated	2002	yes
Diabetes mellitus	porcine, fetal islet cells	10/10	S	Phase 1/ 2	short-term reduction of requirement for exogenous insulin	1994	no

Table 4.7 continued

Disease	Type of cell/tissue/organ	Patients treated/planned	Country	Clinical trial phase	Results	Year	Study pursued further
Diabetes mellitus	porcine neonatal islet cells in microcapsules	6	NZ	Phase 1	reduction of requirement for exogenous insulin for up to 2 years (result not published in peer-reviewed journal)	1999	?
Diabetes mellitus	porcine islet cells (Microcapsules)	20 (?)/24	USA	Phase 1	no requirement for exogenous insulin in 1 patient for 1 month (result not published in peer-reviewed journal)	1999	yes
Diabetes mellitus	fetal islet cells from rabbits	several 100/?	RUS, China	Phase 1/ 2	?	before 1999	?
Diabetes mellitus	porcine islet cells in vascularised collagen tube	12/12	Mexico	Phase 1	1 patient has stopped taking insulin	2001	yes
Parkinson	porcine, fetal neurons	30/30 0/36	USA	Phase 2/3 Phase 3	improvement of clinical symptoms in some cases, but difficult to differentiate from placebo effects, severe side effects in some cases	2001	yes
Parkinson	Cotransplantation of porcine fetal neurons and a mouse cell line (genetically modified, macrocapsules)	0/?	?	planning stage	not yet available	2001	?
Epilepsy	porcine, fetal neurons	3/6	USA	Phase 1	not yet available	2001	yes
Spinal cord injuries	porcine, fetal neural cells	0/6	USA	planned	not yet available	2001	?
Stroke	porcine, fetal neurons	5/6	USA	Phase 1	2 adverse events, trial halted	2001	?
Huntington	porcine, fetal neurons	12/12	USA	Phase 1	Symptomatic improvement in 3 patients, disease progression in 7 patients, 2 patients died of Huntington's disease	2000	no
Huntington	Cotransplantation of porcine fetal neurons and a mouse cell line (genetically modified, macrocapsules)	0/?	?	planning stage	not yet available	2001	?

Disease	Type of cell/tissue/organ	Patients treated/planned	Country	Clinical trial phase	Results	Year	Study pursued further
Severe burns	porcine skin	15	DE	?	?	before 1999	?
solid metastasing tumors	Vero-IL2 (genetically modified non-human primate cell line)	11/?	CH	Phase 1	well tolerated	2000	?
HIV	baboon bone marrow	1	USA	Phase 1/ 2	short-time improvement of clinical symptoms, after few weeks no baboon cells detectable any more	1995	no
"Immunotherapy"	spleen from slaughterhouse pigs (extracorporal perfusion)	100	RUS	?	?	before 1999	?
Amyotrophic lateral sclerosis	Baby Hamster Kidney cell line (genetically modified, macrocapsules)	6/6	CH	Phase 1	well tolerated, no significant clinical improvement	1996	?
Chronic pain	chromaffine bovine cells (macrocapsules)	ca. 100/ca. 150	USA, CH, PL, CZ	Phase 1/ 2	no significant clinical improvement	1996	no
Chronic pain	porcine, fetal neurons	0/6	USA	Phase 1	not yet available	2000	?

Source: Hüsing et al. 2001; Taniguchi et al. 1997, with additions5. International activities in xenotransplantation

5. International regulatory initiatives

In this chapter, a non-exhaustive overview of international activities in xenotransplantation is given. Activities of selected organizations and countries are described in the following subchapters. An overview of their output in terms of reports, positions or regulations is given in table 5.1; in this table, more countries are included than are described in the subchapters.

5.1 World Health Organisation

The World Health Organisation (WHO) has addressed the issue of risk of infection related to xenotransplantation and its policy implications. The WHO has published several reports, based on expert workshops and consultations, conducted a joint OECD/WHO Consultation on Xenotransplantation Surveillance and initiated an Electronic Discussion Group on International Xenotransplantation Policy Considerations. These activities resulted in the publication of WHO guidance xenogeneic infection/disease surveillance and response. WHO has published to following reports:

- *Xenotransplantation: guidance on infectious disease prevention and management* (WHO/EMC/ZOO/98.1)[8]. This report covers the following topics: Contagious Disease Potential of Xenotransplantation; Risk of exposure; Establishment of an agent in individual recipients; Risk of dissemination to the general population; Risk of disease production in the general population
- *Report of WHO Consultation on Xenotransplantation.* Geneva, Switzerland, 28-30 October 1997 (WHO/EMC/ZOO/98.2)[9]. This report covers the following topics: Current Directions in Xenotransplantation Research and Technology Development, Xenozoonotic Disease Risk and Prevention Issues: Management of Xenozoonotic Risk, Ethical and Social Considerations, Developing Guidelines, Policies and Regulations on Xenotransplantation: Examples of National Approaches; Developing Guidelines, Policies and Regulations on Xenotransplantation: Example of an International Approach, the Council of Europe; Conclusions; Recommendations to Member States and to WHO
- *OECD/WHO Consultation on Xenotransplantation Surveillance: Summary* (WHO/CDS/CSR/EPH/2001.1)[10]. This report covers the following topics: Surveillance Issues in Xenotransplantation; Ethical considerations in xenotransplantation surveillance; Tools and characteristics desirable for xenotransplantation surveillance; Developing a concept framework for international xenotransplantation surveillance; Results from Working Group discussions on international xenotransplantation surveillance; Consultation conclusions and recommendations.

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[8] http://www.who.int/emc-documents/zoonoses/docs/whoemczoo981.pdf
[9] www.who.int/emc-documents/zoonoses/ docs/whoemczoo982.pdf
[10] http://www.who.int/emc-documents/zoonoses/docs/whocdscsreph20011.pdf

- *WHO Guidance on Xenogeneic Infection/Disease Surveillance and Response: A Strategy for International Cooperation and Coordination* (WHO/CDS/CSR/EPH/2001.2)[11]. The guidance comprises the following topics: Introduction into xenotransplantation, infectious disease risks, and surveillance; Surveillance Concepts Relevant to Xenotransplantation and Xenogeneic Infection/Disease; An International Surveillance Network for Xenogeneic Infection/Disease Event Surveillance and Response.

The WHO was one of the first international organisations to engage actively in the xenotransplantation subject. The main focus of WHO has been the risk of infection. The WHO has urged that xenotransplantation be treated with extreme caution as the consequences of emergent new infection could be high. The WHOsupports the international consensus that it is ethically unacceptable for a country to allow xenotransplantation to proceed within its borders without it being subject to regulatory oversight and control. Therefore, WHO strongly urges member states to urgently introduce regulations that allow oversight of xenotransplantation. The WHO is willig to facilitate the introduction of such regulation by ist member states and to provide technical assistance by actions such as considering drafting model regulation, and by supporting international cooperation and coordination.

5.2 Organisation for Economic Co-operation and Development

The Organisation for Economic Co-operation and Development (OECD) has addressed the issue of XTP within its activities related to scientific, industrial and health applications of biotechnology. This xenotransplantation activity seeked to develop, together with the World Health Organisation, standards for surveillance following transplantation and for the import/export of transgenic organs and animals. The following activities were carried out within this initiative:

- Publication of two reports as introduction into the subject (OECD 1999; Ronchi 1996)
- Workshop on International issues in transplantation biotechnology including the use of non-human cells, tissues and organs, New York 1998
- Compilation of regulatory developments in xenotransplantation in OECD Member States, status year 2001[12]
- OECD/WHO Consultation on Xenotransplantation Surveillance, 4-6 October 2000 . It had been suggested that a first step towards global co-operation on xenotransplantation surveillance could be furthered through the development of internationally agreed

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[11] http://www.who.int/emc-documents/zoonoses/docs/whocdscsreph20012.pdf, accessed April 23, 2004

[12] http://www.oecd.org/countrylist/0,2578,en_2649_34537_1783767_1_1_1_1,00.html, accessed April 23, 2004

guidance on reporting norms, and use of compatible information technology. This consultation addressed this suggestion by:

- facilitating national and international policy considerations on the desirability, purpose, structures and functions of xenotransplantation surveillance, taking into account the different applications of xenotransplantation;
- reviewing current surveillance systems as operational models for the design of xenotransplantation surveillance;
- considering what technical, information and logistic elements might be useful in support of effective international xenogeneic infection/disease surveillance.

A report has been published[13] which summarises the topics, issues and considerations discussed at the OECD/WHO Consultation on Xenotransplantation Surveillance. The Consultation was held in Paris at OECD Headquarters on 4-6 October 2000 and was attended by over 60 participants from around the world, representing countries currently hosting xenotransplantation clinical trials; countries not actively engaged in xenotransplantation research but interested in its potential public health impact; and relevant international bodies such as the Council of Europe and the European Commission.

The OECD activities in the field of XTP focus on providing an overview of the scientific progress in the field, of policy considerations on xenotransplantation to be addressed, and of current regulatory frameworks in its member states. It also facilitates international cooperation and coordination.

5.3 Vatican

The Catholic Church has addressed the issue of XTP in September 2001 when The Pontifical Academy for Life[14] published the document "Prospects for Xenotransplantation - Scientific Aspects and Ethical Considerations"[15]. It covers the following aspects: The first part gives an introduction into Scientific Aspects, Historical background, Current Situation, Moving to the clinical phase. The second part elaborates Anthropological and Ethical Aspects, especially

- the acceptability of man's intervening in the order of the creation;

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[13] http://www.olis.oecd.org/olis/2001doc.nsf/43bb6130e5e86e5fc12569fa005d004c/7d4e7b2820d508dfc1256af1005328fc/$FILE/JT00115450.PDF; Document No. DSTI/STP/BIO(2001)11/FINAL

[14] http://www.vatican.va/roman_curia/pontifical_academies/acdlife/index.htm

[15] http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20010926_xenotrapianti_en.html; accessed April 23, 2004

- the ethical feasibility of using animals to improve the chances for survival and well-being of human beings;
- the possible objective and subjective impact that an organ or tissue of animal origin can have on the identity of the human recipient
- Bioethical Issues, such as the assessment of the health risk, reflections on transgenesis of animals and its ethical implications, the subject of informed consent, health care resources and economic resources required for XTP, patentability of inventions in xenotransplantation
- Practical Guidelines are given which are intended to guide the path of research and development in the area of xenotransplantation as applied to man: Trials involving humans should only begin if sufficient results have been obtained during preclinical research, and high standards should be complied with. Moreover, a broad public debate is seen as desirable as well as the exploration of alternatives to xenotransplantation.

All in all, the Catholic Church supports XTP, provided that the following aspects can be solved: overcoming scientific-technical hurdles, and dealing with concerns about xenotransplantation that require theological, anthropological, psychological and ethical considerations, as well as an examination of legal issues and procedural matters. It is recommended that a substantial convergence of international legislation in this area should be achieved as soon as possible, by means of a genuine coordination at the different levels. On the one hand such legislation must provide rules for the continuation of scientific research, guaranteeing its validity and safety; on the other hand it must watch over the health of the citizens involved and the potential risks (especially infective) connected with xenotransplantation. Furthermore it must offer criteria for organizing the necessary information campaigns aimed at the entire population.

5.4 Council of Europe

The Council of Europe is the continent's oldest political organisation, founded in 1949. Since 1997, the Council of Europe's work has been strenghtened in four areas: democracy and human rights, social cohesion, the security of citizens and democratic values and cultural diversity. It issues legally binding European treaties or conventions (e. g. human rights) and gives recommendations to governments setting out policy guidelines on such issues as legal matters, health, education, culture and sport. It is – among others – engaged in the fields of biomedicine, organ transplantation and bioethics[16].

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[16] http://www.coe.int/T/E/Legal%5FAffairs/Legal%5Fco%2Doperation/Bioethics/; accessed April 23, 2004

In 1997, the Committee of Ministers adopted Recommendation No R(97)15 to member states on xenotransplantation[17]. It recommended that governments of member States should establish a mechanism for the registration and regulation of the following aspects of xenotransplantation with a view to minimising the risk of transmission of known or unknown diseases and infections to either the human or animal population:

- basic research and clinical trials;
- the source and care of animals for use in xenotransplantation;
- xenotransplantation programmes;
- long term follow-up and review of xenograft recipients and the xenograft source animals.

The Parliamentary Assembly of the Council of Europe, having considered the risks of infection to public health which xenotransplantation could involve, stated that it was in favour of a moratorium on the clinical applications of xenotransplantation and asked the Committee of Ministers to initiate a study relating to the different aspects of the relevant issues (Recommendation 1399 (1999) on xenotransplantation).

Without taking a stance on the proposition of a moratorium, the Committee of Ministers established a Working Party under the bilateral authority of the Steering Committee on Bioethics (CDBI) and the European Health Committee (CDSP). Chaired by Mr. Bart Wijnberg (The Netherlands), the Working Party drafted an interim report on "The State of the Art in the Field of Xenotransplantation", published in 2000. A revised version has been published in 2003 (Council of Europe 2003).

The Working Party also finalised draft guidelines on xenotransplantation which were approved by the Steering Committee on Bioethics (CDBI) and the European Health Committee (CDSP) in June 2002. These guidelines were adopted by the Committee of Ministers in June 2003 (Recommendation Rec(2003)10 on xenotransplantation[18][19]. This recommendation aims to protect, in both the short and long term, public health, patients, their close personal contacts and the professional staff involved in xenotransplantation, and to provide adequate protection for the animals used in xenotransplantation.

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[17] Recommendation No R(97)15 of the Committee of Ministers to member states on xenotransplantation (adopted by the Committee of Ministers on 30 September 1997, at the 602nd meeting of the Ministers' Deputies); http://www.coe.int/T/E/Social%5FCohesion/Health/Recommendations/Rec(1997)15.asp#TopOfPage, accessed April 23, 2004

[18] http://www.coe.int/T/E/Social_Cohesion/Health/Documentation/Rec(2003)10.asp#TopOfPage; accessed April 23, 2004

[19] http://www.coe.int/T/E/Social%5FCohesion/Health/

It recommends that no xenotransplantation should be carried out in a member state that does not provide regulation for xenotransplantation activities in conformity with the provisions of this recommendation. The following provisions are given:

- No xenotransplantation activity should be carried out in a member state unless authorisation is given by a body officially recognised as competent for this purpose. Authorisation may only be granted if there is no risk of infection for public health and efficacy and safety for the patient justifies the intervention.
- Xenotransplantations should only be carried out by an accredited team in an authorised centre.
- A public health protection plan should be in place, information and biological samples concerning the source animals used in xenotransplantation and the recipients should be collected and stored in order to ensure traceability and long-term monitoring, and a follow-up and monitoring after XTP should be established.
- Precautions relating to the transmission of disease comprise the exclusive use of animals bred specifically for xenotransplantation under appropriate Quality Assurance systems, the prohibition to use non-human primates as source animals for organs
- Conditions for patient participation comprise that there is no other appropriate therapeutic method of comparable effectiveness available for the patient, that a clear therapeutic benefit can reasonably be expected for the patient, and that the risks which may be incurred by the patient are not disproportionate to the potential therapeutic benefit of the procedure.
- Information to be given to patients participating in a xenotransplantation should comprise the the nature, objectives, possible benefits, potential risks and consequences of the procedure, as well as of any constraints that may be linked to it, especially of the constraints of monitoring and precautionary measures that may become necessary subsequent to xenotransplantation.
- Information to be given to close contact persons of the patient and to the professional staff involved in xenotransplantation
- Xenotransplantations should only be performed if the patient has given his specific, free and informed consent; patients not able to consent may only be treated with xenotransplantation under strict conditions
- Patients and their close personal contacts should have access to independent counselling and support by experts, and the option of xenotransplantation treatment should not prejudice the patient's right to receive all other appropriate medical care in due course
- Moreover, provisions for the protection of animals are given.

- Member states should take active steps to ensure that the fundamental questions raised by xenotransplantation are the subject of appropriate public discussion particularly in light of relevant medical, psychological, cultural, ethical, legal, social and economic implications
- Member states should co-operate internationally in medical research and public health (e. g. international surveillance procedures and agreements, co-ordination of research in xenotransplantation).

All in all, the Council of Europe is of opinion that XTP should only be carried out in a member state if appropriate regulatory oversight has been established. Moreover, it gives concrete guidance how this regulatory oversight should be shaped. This guidance takes all XTP aspects into account that have been discussed internationally in the previous years.

5.5 European Union

During 1999 the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) discussed a list of emerging issues of public health importance related to medical treatment and likely concern in the future. Xenotransplantation was one of these which carried a high priority and a working group was therefore established to scope the issue. An opinion was published in 2001 which had the purpose to report to the European Commission (DG SANCO) the current developments and concerns in the field of XTP and to identify issues that may require community-wide action. The following recommendations were made with respect to the therapeutic use of xenotransplantation (European Commission Health & Consumer Protection Directorate-General 2001):

- The European Commission should propose the establishment of a centralised regulatory body to oversee the process and to minimise the risks,
- the European Commission should carry out a thorough and ongoing risk analysis of XTP on the basis of the results of both research and clinical trials,
- specific measures for clinical trials dealing with authorisation, informed consent, registration, surveillance of patients and those at risk should be defined on the basis of Directive 2001/20/EC (),
- appropriate quality requirements related to health status, animal welfare and animal production should be defined and implemented for the XTP source animals,
- appropriate quality requirements for procurement of organs and their clinical use should be formulated and implemented for centres performing XTP,
- requirements for surveillance should be defined and implemented for the source animals, XTP recipients and others at risk,

- the European Commission should stimulate and support research on detecting and understanding the risks of viral infections with respect to XTP, and the risks associated with severe immunosuppressive drug therapy, especially relating to interference with other drug therapy.

The European Commission has divided the regulation of substances of human origin in three categories: (1) organs, (2) tissues and cells, and (3) blood[20]. Up to now, blood is the only category that has detailed European wide legislation in place.

Regarding the regulation of tissues and cells, a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells has been adopted by the Council on March 2, 2004, but this directive does not apply to xenogeneic tissues and cells. However, at least for therapeutic applications of cellular xenotransplantations, a legally binding framework has been established: xenogeneic cell therapy has been included into the Annex I (Part IV) to the EU Directive on medicinal products (Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC relating to medicinal products for human use). In this way, regulatory oversight is formally established and an authorisation according to medicinal products will be required prior to clinical use. In order to establish guidance how this evaluation and authorisation should be performed, the European Agency for the Evaluation of Medicinal Products (EMEA) has recently adopted points to consider on xenogeneic cell therapy medicinal products (EMEA et al. 2003), after a concept paper on the development of points to consider on xenogeneic cell therapy had been issued in 2000 (EMEA 2000). The points to consider take into account requirements for sourcing of animals, manufacturing of the xenogeneic cells, non-clinical testing, proof of human efficacy and safety, as well as pharmacovigilance and special surveillance methods.

In 2004, a regulation is being developed by the European Commission which will cover the placing on the market of human tissue engineered products[21]. The scope of this draft regulation has been restricted to human cells and the use of xenogeneic cell and tissue sources has been deliberately excluded from the scope of the regulation for the time being but might be included some time after the regulation would have been implemented[22]. One reason is that there are no tissue engineered products based on xenogeneic cell sources yet which are close to market introduction. Another reason is that the inclusion of xenogeneic cell and tissue sources into the regulation would require an intensive parliamentary debate which would most likely delay the adoption of this regulation significantly.

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[20] http://europa.eu.int/comm/health/ph_threats/human_substance/blood_tissues_organs_en.htm; last visited 27 February 2004

[21] http://pharmacos.eudra.org/F3/human-tissue/index.htm

[22] http://pharmacos.eudra.org/F3/human-tissue/Consultation_document.pdf, p. 6

The regulation of the use of human organs for transplantation has not yet been addressed at the EU level, their use is regulated on Member State level. However, the Commission, under article 152 of the Amsterdam Treaty, will consider the need to identify, monitor and control the factors influencing the quality and safety of organs used for transplantation at European Union level. It is not known whether this consideration will also comprise XTP.

At present, the European Union has not yet engaged in a comprehensive debate on XTP. It has only put into place regulations for medicinal products such as cell therapies which contain xenogeneic cells. This regulation requires that such therapies are subject to an authorisation procedure by a competent authority. Therefore, it is in the responsibility of EU Member States to deal with XTP, drawing on guidance from e. g. the Council of Europe and the WHO.

5.6 United Kingdom

The United Kingdom was one of the first countries which engaged in a discussion of the promises and risks of xenotransplantation. This may also be due to the fact that one of the leading companies in XTP, Imutran Ltd., at that time was located in the UK and in 1995 had announced to perform first clinical XTP trials soon. In late 1995, the Advisory Group on the Ethics of Xenotransplantation was formed under the Chairmanship of Professor Ian Kennedy. This commenced UK work on xenotransplantation and its implications. The Advisory Group's report to Government, Animal Tissue into Humans, was published in January 1997 (The Advisory Group on the Ethics of Xenotransplantation 1996). Its main conclusion was that xenotransplantation could be acceptable provided that certain criteria were met. Amongst more than sixty detailed recommendations, was a recommendation for the establishment of a regulatory body to oversee the development of xenotransplantation in this country. The Nuffield Council on Bioethics has also been active in the field of XTP[23]. Nearly at the same time as the Kennedy Commission, the Nuffield Council on Bioethics set up a Working Party to examine ethical questions of XTP, held a public consultation and a report was published in March 1996. The report considered concerns such as:

- is it ethical to use animals to provide 'spare parts' for humans?
- is it ethical to produce genetically modified pigs containing human genes?
- how can any animal suffering be minimised?
- will animal diseases be passed onto human beings?
- how can early patients be protected?

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[23] http://www.nuffieldbioethics.org/xenotransplantation/index.asp; accessed April 23, 2004

- could the National Health Service afford animal-to-human transplants?

The Report gave cautious approval to xenotransplantation, recommending that development of animal-to-human transplants should continue, subject to rigorous regulation. Similar to the Kennedy Commission, the Report also called on the Government to establish an Advisory Committee on Xenotransplantation to regulate developments (Nuffield Council on Bioethics 1996).

The United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA)[24] was established in response to the Kennedy report (UK Government 1997). The UKXIRA, chaired by Lord Habgood of Calverton, the former Archbishop of York, met for the first time on 17 May 1997 and currently meet four times a year.

UKXIRA's terms of reference are:

"To advise the Secretaries of State for Health, Northern Ireland, Scotland and Wales on the action necessary to regulate xenotransplantation, taking into account the principles outlined in "Animal Tissues into Humans", and worldwide developments in xenotransplantation. In particular to advise:

(a) on safety, efficacy and considerations of animal welfare in liaison with the Home Office, and any other pre-conditions for xenotransplantation for human use, and whether these have been met;

(b) on research required to assess safety and efficacy factors in xenotransplantation procedures;

(c) on the acceptability of specific applications to proceed with xenotransplantation in humans; and

(d) to provide a focal point on xenotransplantation issues within Government."

The following reports have been published by UKXIRA:

- Draft guidance notes on biosecurity considerations in relation to xenotransplantation
- Draft report of the Infection Surveillance Steering Group of the UKXIRA
- The Physiology of Xenotransplantation
- Infection risks in xenotransplantation

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[24] http://www.advisorybodies.doh.gov.uk/ukxira/index.htm, accessed April 23, 2004

- Report of the workshop on porcine endogenous retroviruses
- Guidance on making proposals to conduct xenotransplantation on human subjects
- Law & Ethics of Xenotransplantation - Bibliography and Abstracts of Key Articles (until 2002)

All in all, XTP is seen by the Government as a potential solution to the organ donor shortage. Regulatory oversight and the development of guidance by the UKXIRA has been established in order to deal with its complex ethical issues, and issues such as safety - both to the individual and the wider public; of the efficacy of such procedures; and considerations of animal welfare.

5.7 The Netherlands

A public debate about xenotransplantation was being held in the Netherlands from 2000-2001[25]. Further to a debate, held in the Dutch Lower House in February 2000, the Dutch government prepared a temporary ban on xenotransplantation. The House also pressed for a public debate on xenotransplantation. To this end, the Dutch Ministry of Health, Welfare and Sports assigned C&B with the task to realize this. The aim was to provide citizens with unbiased information on the various aspects of xenotransplantation, but also of other new developments in the field of organ donation and transplantation. This in turn, should enable them to form and express opinions on the subject.

The debate commenced in November 2000, and ended April 2001. The activities comprised an internet website, public meetings, science theatre, a public survey and a cartoon brochure. They were organised in such a way that citizens were able to inform themselves about xenotransplantation, and enter into debates with others on the subject. The following themes were addressed:

- General information about what xenotransplantation is.
- The shortage of donor organs: a reason to develop xenotransplantation.
- Other solutions that are being developed to solve the donor organ shortage.
- The risks of xenotransplantation for humans.
- Does a human to some extent become an animal after xenotransplantation?
- The consequences of xenotransplantation for the animals involved.

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[25] http://www.xenotransplantatie.nl

- The role of government and politicians in the decision-making process on the development and application of xenotransplantation.
- Opinions about xenotransplantation from the various people and organisations concerned.

The final report (The Dutch Consumer and Biotechnology Foundation 2001) was presented to the Minister of Health in August 2001[26]. In 2002, the two-year moratorium on xenotransplantation was transformed into a ban of xenotransplantation (Wet op bijzondere medische verrichtingen; Staatsblad 2002, 263). Thus, the Netherlands is one of the few countries which have implemented a ban on XTP.

5.8 Australia

In 2001, National Health and Medical Council established a Xenotransplantation Working Party to investigate whether research into xenotransplantation should be allowed in Australia. In July 2002, the Working Party released a Discussion Paper which provided background information in order to allow informed community discussion. It also contained draft guidelines. In 2002, written comments to these draft guidelines were invited, and also public meetings were held. A second round comprised public meetings in all capital cities during February 2004. The following documents have been developed by the Working Party to inform these two rounds of consultation:

- Draft guidelines and discussion paper on xenotransplantation (A document prepared to informed the first round of public consultation in 2002)[27]
- Animal-to-human transplantation research: A guide for the community[28]
- Animal-to-human transplantation research: How should Australia proceed? (Response to the 2002 public consultation on Draft guidelines and Discussion Paper on xenotransplantation)[29]

The policy making process is still on-going at the time of writing this report (April 2004). Therefore, results from this process cannot yet be reported.

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[26] http://www.xenotransplantatie.nl/uk2.pdf, accessed April 23, 2004
[27] http://www.nhmrc.gov.au/issues/xeno.pdf
[28] http://www.nhmrc.gov.au/publications/pdf/e54.pdf
[29] http://www.nhmrc.gov.au/publications/pdf/e55.pdf

5.9 USA

In the USA, the U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) is responsible for the regulation of xenotransplantation[30]. The authority aims at providing a comprehensive regulatory approach that addresses the potential public health safety issues associated with xenotransplantation and to provide guidance to sponsors, manufacturers and investigators regarding xenotransplantation product safety and clinical trial design and monitoring. Its activities comprise

- the establishment of a Xenotransplantation Product Reviewer Working Group, consisting of the review staff responsible for the review of xenotransplantation clinical trial submissions and xenotransplantation product xenotransplantation applications
- Conducting scientific investigations and research in order to widen the understanding of safety issues associated with xenotransplantation
- Sponsoring, planning or participating in numerous open public meetings and workshops, both domestic and international that focused in whole or in part on xenotransplantation.
- Formation of the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (BRMAC) in 1997 as an ongoing mechanism for open discussions of the scientific, medical, social, and ethical issues and the public health concerns raised by xenotransplantation, as well as specific ongoing and proposed protocols
- Establishment of the DHHS Secretary's Advisory Committee on Xenotransplantation (SACX), in order to consider the full range of complex scientific, medical, social, ethical, and public health concerns raised by xenotransplantation, and make recommendations to the Secretary on policy and procedures

The following documents have been published:

- Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (April 3, 2003)[31]
- Human Cells or Tissues Intended for Transplant Into a Human Recipient That Have Ex-vivo Contact With Live Nonhuman Animal Cells, Tissues, or Organs (Letter of March 8, 2002)[32]

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30 http://www.fda.gov/cber/xap/xap.htm, accessed April 23, 2004
31 http://www.fda.gov/cber/gdlns/clinxeno.pdf
32 http://www.fda.gov/cber/ltr/humemb.pdf

- Information and Recommendations for Physicians Involved in the Co-Culture of Human Embryos with NonHuman Animal Cells (March 8, 2002)[33]
- Draft 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 Intimate Contacts (February 1,2002)[34]
- PHS Guideline on Infectious Disease Issues in Xenotransplantation (January 19, 2001)[35]
- Guidance For Industry: Public Health Issues Posed by the Use of Non-Human Primate Xenografts in Humans (April 6, 1999)[36].

All in all, the USA has taken a positive position towards XTP. Important players in the XTP field conduct their R&D in the USA, and regulatory oversight has been developed and established by the FDA.

5.10 Canada

Health Canada's Therapeutic Products Programme (TPP) is the national authority which regulates drugs, medical devices and other therapeutic products used in Canada. Xenotransplants are regulated by Health Canada under the requirements of the Food and Drugs Act.

In November 1997, the TPP sponsored a National Forum on Xenotransplantation in Ottawa. This Forum represented the first national consultation on the scientific, ethical and regulatory issues surrounding xenotransplantation. The Forum summary report included several important recommendations, such as the need to inform the public about xenotransplantation, to involve the public in the policy development process and to develop safety standards that can be used to regulate xenografts if and when they are approved for use in Canada.

The TPP has established an Expert Working Group, comprised of experts in the areas of transplantation, infectious disease, veterinarian medicine and ethics, to develop a safety standard for xenotransplantation. In July 1999, the TPP released, for public comment, the draft Proposed Standard for Xenotransplantation, which identifies important issues that should be addressed for the safety and effectiveness of xenotransplantation.

In March 1999, the TPP conducted a public opinion survey as an early scan of Canadian's level of knowledge of xenotransplantation and their interest in participating in the decision-

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[33] http://www.fda.gov/cber/infosheets/humembclin.htm
[34] http://www.fda.gov/cber/gdlns/zoobldxeno.pdf
[35] http://www.fda.gov/cber/gdlns/xenophs0101.pdf
[36] http://www.fda.gov/cber/gdlns/xenoprim.pdf

making process. The survey showed a broad public support for XTP, but most of the respondents indicated that they were not knowledgeable about XTP issues and that a large percentage of respondents wanted to be involved in some way (e. g. kept informed, invited to comment, involved in meetings). The TPP developed a Public Involvement Plan for Xenotransplantation and sponsored a Planning Workshop, in April 2000, to obtain public input to the plan. The Planning Workshop: Public Involvement for Xenotransplantation, brought together a broad range of people interested in and affected by xenotransplantation, to discuss elements of the Public Involvement Plan, including the formation of a Public Advisory Group and processes to broaden awareness, information/education and dialogue of xenotransplantation among Canadians.

As a step toward implementing the Public Involvement Plan, in 2000, Health Canada funded the Canadian Public Health Association, a national, independent, not-for-profit, voluntary association representing public health in Canada, to form a Public Advisory Group on Xenotransplantation and to undertake conduct a public consultation on xenotransplantation. The aim was to consult with the Canadian public on the health, ethical, legal, economic and social issues related to xenotranstransplantation and to report to the Minister of Health on the results of those consultations so that the views of Canadians will help to guide the future development of government policy on xenotransplantation in Canada. The following key issues were addressed in this consultation exercise:

Issue #1: Is xenotransplantation needed?

Issue #2: Is xenotransplantation viable?

Issue #3: How far should we go to save a human life?

Issue #4: Is the risk to the public acceptable?

Issue #5: Are there legal issues that should be considered?

Issue #6: What animal issues need to be considered?

Issue #7: What costs need to be considered?

Issue #8: If Canada proceeds with xenotransplantation, what regulations would need to be in place to manage it?

The results of this public consultation were published in a final report in December 2001[37]. It made the following recommendations on XTP:

- that Canada not proceed with XTP involving humans at this time as there are critical issues that first need to be resolved,

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[37] http://www.xeno.cpha.ca/english/finalrep/reporte.pdf

- that alternatives to XTP, such as prevention, expanding the human donor pool, mechanical substitutes and stem cell research be further explored,
- that the Canadian publik receive more information about organ and tissue donation, healthy lifestyles, disease prevention, and disease management,
- that pre-clinical research continue in order to gain further knowledge about the potential health risks and viability of XTP,
- that stringent and transparent legislation and regulations be developed to cover all aspects of XTP clinical trials,
- that the public continue to be informed and involved in discussions about the future of XTP,
- That the citizen form model be strongly considered for future consultations on complex and not widely understood policy issues.

In addition, the Expert Advisory Committee (EAC) on Xenograft Regulation was formed to provide the Biologics and Genetic Therapies Directorate with timely advice on our medical, scientific, ethical and communication issues related to the regulation of xenografts. Collectively, the EAC members provide health professional and related expertise and advice pertaining to risk/benefit assessments conducted by others within Health Canada in order to assist the Biologics and Genetic Therapies Directorate with making appropriate risk management decisions. The decision-making responsibility remains with the Biologics and Genetic Therapies Directorate.

Table 5.1: Non-exhaustive overview of international opinions, reports and regulations in the field of xenotransplantation

Supranational Organisation; Country	Opinions, reports and regulations
World Health Organization (WHO)	WHO (1998): Xenotransplantation: Guidance on Infectious Disease Prevention and Management. WHO/EMC/ZOO/98.1. World Health Organization: Geneva, Switzerland (http://www.who.int/emc-documents/zoonoses/docs/whoemczoo981.pdf)
	WHO (1997): Report of WHO Consultation on Xenotransplantation. World Health Organization, Geneva, Switzerland, 28-30 October 1997 (http://www.who.int/emc-documents/zoonoses/ docs/whoemczoo982.pdf)
	WHO/OECD (2001): OECD/WHO Consultation on Xenotransplantation Surveillance: Summary (WHO/CDS/CSR/EPH/2001.1) (http://www.who.int/emc-documents/zoonoses/docs/whocdscsreph20011.pdf)
	WHO Guidance on Xenogeneic Infection/Disease Surveillance and Response: A Strategy for International Cooperation and Coordination (WHO/CDS/CSR/EPH/2001.2) (http://www.who.int/emc-documents/zoonoses/docs/whocdscsreph20012.pdf)
Organization for Economic Cooperation and Development (OECD)	OECD (1996): Advances in Transplantation Biotechnology and Animal to Human Organ Transplants (Xenotransplantation). Paris
	OECD (1999): Xenotransplantation. International Policy Issues. OECD Proceedings. Paris
	OECD/WHO (2001): OECD/WHO Consultation on Xenotransplantation Surveillance. Summary. Held in Paris on 4-6 October 2000. Document No. DSTI/STP/BIO(2001)11/FINAL. Paris: OECD (http://www.olis.oecd.org/olis/2001doc.nsf/43bb6130e5e86e5fc12569fa005d004c/7d4e7b2820d508dfc1256af1005328fc/$FILE/JT00115450.PDF)
Vatican	Pontifical Academy for Life (2001): Prospects for Xenotransplantation - Scientific Aspects and Ethical Considerations. Rome: Pontifical Academy for Life (http://www.vatican.va/roman_curia/pontifical_academies/acdlife/index.htm)
International Xenotransplantation Association	Sykes, M.; d'Apice, A.; Sandrin, M. et al. (2003): Position paper of the Ethics Committee of the International Xenotransplantation Association. In: Xenotransplantation, Vol. 10, pp. 194-203
International Society of Heart and Lung Transplantation	Cooper, D. K. C.; Keogh, A. M.; Brink, J. et al. (2000): 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. In: The Journal of Heart and Lung Transplantation, Vol. 19, pp. 1125-1165

Table 5.1 continued

Supranational Organisation; Country	Opinions, reports and regulations
Council of Europe	Recommendation No R(97)15 of the Committee of Ministers to member states on xenotransplantation (adopted by the Committee of Ministers on 30 September 1997, at the 602nd meeting of the Ministers' Deputies); http://www.coe.int/T/E/Social%5FCohesion/Health/Recommendations/Rec(1997)15.asp#TopOfPage, accessed April 23, 2004
	Council of Europe, Parliamentary Assembly (1999): Xenotransplantation. Recommendation 1399 (1999) (1). Provisional edition January 1999
	Council of Europe, Committee of Ministers (1999): Reply from the Committee of Ministers to Recommendation 1399 (1999), Xenotransplantation. Doc. 8393, 25. März 1999. http://stars.coe.fr/doc/doc99/edoc8363.htm
	CDBI/CDSP-XENO (2000): State of the art report on xenotransplantation. Strasbourg, Working Party on Xenotransplantation under the joint responsibility of the Steering Committee on Bioethics and the European Health Committee of the Council of Europe, July 2000 (http://www.coe.fr/dase/en/qoflife/publi/artreport/tableart.htm)
	Council of Europe (2003): Report on the state of the art in the field of xenotransplantation. Strasbourg: Steering Committee on Bioethics (CDBI), European Health Committee (CDSP), 90 p.
	Recommendation Rec(2003)10 of the Committee of Ministers to member states on xenotransplantation (Adopted by the Committee of Ministers on 19 June 2003 at the 844th meeting of the Ministers' Deputies); http://www.coe.int/T/E/Social_Cohesion/Health/Documentation/Rec(2003)10.asp#TopOfPage;%20accessed%20April%2023,%202004
European Commission	Scientific Committee on Medicinal Products and Medical Devices (2001): Opinion on the state of the art concerning xenotransplantation. Doc SANCO/SCMPMD/2001/0002Final. Brussels: Health and Consumer Protection Directorate General, European Commission, October 1, 2001 http:// http://www.europa.eu.int/comm/food/fs/sc/scmp/out38_en.pdf
	EU Directive on medicinal products (Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC relating to medicinal products for human use
	EMEA. (2000): Concept paper on the development of a committee for proprietary medicinal products (CPMP) points to consider on xenogeneic cell therapy. CPMP/BWP/3326/99. Internet-Document, retrieved from www.emea.eu.int/pdfs/human/bwp/332699en.pdf
	EMEA; Committee for Proprietary Medicinal Products (CPMP). (2003): Points to consider on xenogeneic cell therapy medicinal products. CPMP/1199/02. Internet-Document, retrieved from www.emea.eu.int/pdfs/human/bwp/332699en.pdf

Table 5.1 continued

Supranational Organisation; Country	Opinions, reports and regulations
USA	Institute of Medicine (1996): Xenotransplantation. Science, Ethics, and Public Policy. Washington, D.C.: National Academy Press
	Public Health Service (1996): Draft Public Health Service Guideline in Infectious Disease Issues in Xenotransplantation. August 1996
	U. S. Department of Health and Human Services (1999a): Draft Guidance for Industry. Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans. April 1999 (http://www.fda.gov/cber/gdlns/xenoprim.pdf)
	Public Health Service (2000): Guideline on Infectious Disease Issues in Xenotransplantation. (January 19, 2001) (http://www.fda.gov/cber/gdlns/xenophs0101.pdf)
	U. S. Department of Health and Human Services (2002): Draft 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 Intimate Contacts. (February 1,2002) (http://www.fda.gov/cber/gdlns/zoobldxeno.pdf)
	U. S. Department of Health and Human Services (2002): Human Cells or Tissues Intended for Transplant Into a Human Recipient That Have Ex-vivo Contact With Live Nonhuman Animal Cells, Tissues, or Organs (Letter of March 8, 2002) (http://www.fda.gov/cber/ltr/humemb.pdf)
	U. S. Department of Health and Human Services (2002): Information and Recommendations for Physicians Involved in the Co-Culture of Human Embryos with NonHuman Animal Cells (March 8, 2002) (http://www.fda.gov/cber/infosheets/humembclin.htm)
	U. S. Department of Health and Human Services (2003): Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (April 3, 2003) (http://www.fda.gov/cber/gdlns/clinxeno.pdf)
Canada	Health Canada (1997): Report of the National Forum on Xenotransplantation: Clinical, Ethical, and Regulatory Issues. November 6-8, 1997, Health Canada
	Health Canada, The Expert Working Group on Xenotransplantation (1999): Proposed Canadian Standard for Xenotransplantation. Juli 1999
	Canadian Public Health Association (2001): Animal-to-human transplantation: Should Canada proceed? A public consultation on xenotransplantation. Ottawa: Canadian Public Health Association (http://www.xeno.cpha.ca/english/finalrep/reporte.pdf)

Table 5.1 continued

Supranational Organisation; Country	Opinions, reports and regulations
Australia and New Zealand	Transplantation Society of Australia and New Zealand, Inc. (1998): Xenotransplantation: A report to the Research Committee (Public Health and Medical), the National Health and Medical Research Council, from an Ad Hoc Working Party
	Xenotransplantation Working Party (2002): Draft guidelines and discussion paper on xenotransplantation (A document prepared to informed the first round of public consultation in 2002). National Health and Medical Council (http://www.nhmrc.gov.au/issues/xeno.pdf)
	Xenotransplantation Working Party (2003): Animal-to-human transplantation research: A guide for the community. National Health and Medical Council (http://www.nhmrc.gov.au/publications/pdf/e54.pdf)
	Xenotransplantation Working Party (2003): Animal-to-human transplantation research: How should Australia proceed? (Response to the 2002 public consultation on Draft guidelines and Discussion Paper on xenotransplantation). National Health and Medical Council (http://www.nhmrc.gov.au/publications/pdf/e55.pdf)
Germany	Kirchenamt der Evangelischen Kirche in Deutschland, Sekretariat der Deutschen Bischofskonferenz (Hrsg.)(1998): Xenotransplantation – Eine Hilfe zur ethischen Urteilsbildung. Gemeinsame Texte 13. Mitglieder der AG: D. von Engelhardt, J. Fischer, W. Kernstock-Jörns, J. Reiter, H. J. Schlitt, K. Seelmann. Hannover, Bonn 1998
	Bundesärztekammer (1999): Stellungnahme des wissenschaftlichen Beirates der Bundesärztekammer zur Xenotransplantation. Deutsches Ärzteblatt 96 (29-29), B-1541-B-1547
	Petermann, Th., Sauter, A. (1999): TA-Monitoring "Xenotransplantation". Sachstandsbericht. TAB-Arbeitsbericht Nr. 64. Berlin: Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag
France	National Consultative Ethics Committee for Health and Life Sciences (CCNE) (1999): Opinion on Ethics and Xenotransplantation; No. 61, June 11,1999 http://www.ccne-ethique.org/english/start.htm
Italy	Opinion of the National Bioethics Committee on the proposal for a moratorium on human xenotransplantation trials (1999); http://www.palazzochigi.it/bioetica/english/xeno.html
	Consiglio Superiore di Sanità (CSS)(2002): Linee-guida per la Sperimentazione Clinica degli Xenotrapianti. Rome: Ministerio della Salute
Spain	Organización Nacional de Trasplantes. Ministerio de Sanidad y Consumo: Xenotransplantation. Recommendations for the Regulation of Xenotransplantation Activities in Spain. Extracted from the Report of the Xenotransplantation Commission of the National Transplant Commission. Ed. Complutense, S. A., Madrid February 1999

Table 5.1 continued

Supranational Organisation; Country	Opinions, reports and regulations
United Kingdom	Nuffield Council on Bioethics. (1996): Animal-to-Human Transplants. The ethics of xenotransplantation. London: Nuffield Council on Bioethics.
	Advisory Group on the Ethics of Xenotransplantation (Kennedy Report) (1997): Animal Tissue into Humans. (Finished 1996, publ. 1997) London: Department of Health, 257 p.
	United Kingdom Department of Health (1997): The Government Response to "Animal Tissue Into Humans", the Report of the Advisory Group on the Ethics of Xenotransplantation. London: The Stationary Office, UK Government.
	Uncaged Campaigns (1998): The Science and Ethics of Xenotransplantation. S. Beddard & D. Lyons. Sheffield
	United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) (1998): Report of the workshop on porcine endogenous retroviruses. London: Department of Health, UKXIRA
	United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) (1998a): Guidance on Making Proposals to conduct Xenotransplantation on Human Subjects. London: Department of Health, UKXIRA
	United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) (1999b): Draft Guidance Notes on Biosecurity Considerations in Relation to Xenotransplantation. London: Department of Health, UKXIRA
	United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) (1999a): Draft report of the Infection Surveillance Steering Group of the UKXIRA. London: Department of Health, UKXIRA
	Home Office; Animals, Byelaws & Coroners Unit (1999): Draft Code of Practice for the Housing and Care of Pigs intended for Use as Xenotransplant Source Animals. London: September 1999
	Muir, D.; Griffin, G. (2001): Infection Risks in Xenotransplantation. London: Department of Health, UKXIRA
	Dobson, J. M.; Dark, J. (2002): The Physiology of Xenotransplantation. London: Department of Health, UKXIRA
	McLean, S.; Williamson, L. (2003): Law & Ethics of Xenotransplantation - Bibliography and Abstracts of Key Articles. London: Department of Health, UKXIRA, http://www.advisorybodies.doh.gov.uk/ukxira/law-ethics-biblio.pdf

Table 5.1 continued

Supranational Organisation; Country	Opinions, reports and regulations
Sweden	The Swedish Committee on Xenotransplantation, Ministry of Health and Social Affairs (1999): From one species to another – transplantation from animals to humans. Summary and Statutory proposal. A Report by the Swedish Committee on Xenotransplantation. Swedish Government Official Report no. 1999:120. Stockholm 1999
	Proposal for an act (2000:000) for clinical trials on humans involving transfer of living biological material from animals (Xeno Licensing and Control Act). In: The Swedish Committee on Xenotransplantation (1999): From one species to another – transplantation from animals into humans. Summary and Statutory proposals. Swedish Government Official Report no 1999:120. Stockholm: Ministry of Health and Social Affairs 1999
	Proposal for a Xenotransplantation Register and Biobank Act (2000:000). In: The Swedish Committee on Xenotransplantation (1999): From one species to another – transplantation from animals into humans. Summary and Statutory proposals. Swedish Government Official Report no 1999:120. Stockholm: Ministry of Health and Social Affairs 1999
	Proposal for Amendment to the Secrecy Act (1980:100). In: The Swedish Committee on Xenotransplantation (1999): From one species to another – transplantation from animals into humans. Summary and Statutory proposals. Swedish Government Official Report no 1999:120. Stockholm: Ministry of Health and Social Affairs 1999
	Proposal for an Ordinance (2000:000) on clinical trials involving the transfer of living biological material from animals (Xeno Licensing and Control Ordinance). In: The Swedish Committee on Xenotransplantation (1999): From one species to another – transplantation from animals into humans. Summary and Statutory proposals. Swedish Government Official Report no 1999:120. Stockholm: Ministry of Health and Social Affairs 1999
	Proposal for an Ordinance (2000:000) on instructions for the Xenotransplantation Board. In: The Swedish Committee on Xenotransplantation (1999): From one species to another – transplantation from animals into humans. Summary and Statutory proposals. Swedish Government Official Report no 1999:120. Stockholm: Ministry of Health and Social Affairs 1999
The Netherlands	Dutch Society for the Protection of Animals (DSPA), Hamakers, I. J., (1997): Xenotransplantartion. Animals reduced to spare organ suppliers. Den Haag
	Health Council of the Netherlands: Committee on Xenotransplantation (1998): Xenotransplantation. Publikation Nr. 1998/01E. Rijswijk: Health Council of the Netherlands
	The Dutch Consumer and Biotechnology Foundation. (2001): Xenotransplantation. Is and should it be possible? Final report in respect of the public debate on xenotransplantation. The Hague: The Dutch Consumer and Biotechnology Foundation, 40 p.
	Ban of xenotransplantation (Wet op bijzondere medische verrichtingen; Staatsblad 2002, 263)

Table 5.1 continued

Supranational Organisation; Country	Opinions, reports and regulations
Switzerland	Basler Appell gegen Gentechnologie (1996): Herz vom Schwein? Risiken der Xenotransplantation beim Menschen. Basel
	Hüsing, B., Engels, E.-M., Frick, T. W., Menrad, K., Reiß, T. (1998): Technologiefolgen-Abschätzung Xenotransplantation. Bern: Schweizerischer Wissenschaftsrat TA 30/1998, Bern
	Hüsing, B.; Engels, E.-M.; Gaisser, S. et al. (2001): Zelluläre Xenotransplantation. Bern: Zentrum für Technologiefolgen-Abschätzung beim Schweizerischen Wissenschafts- und Technologierat
	Schweizerische Akademie der Medizinischen Wissenschaften (1999): Medizinisch-ethische Grundsätze zur Xenotransplantation. Stellungnahme der SAMW. Basel
	Schweizerischen Akademie der Medizinischen Wissenschaften SAMW, Schweizerischen Akademie der Naturwissenschaften SANW, Ethikkommission für Tierversuche (2000): Beitrag zur ethischen Beurteilung der Xenotransplantation im Hinblick auf den Schutz der Würde der Tiere. Schweizerische Ärztezeitung. 81 (1), 36-37
	Bundesgesetz betreffend die Änderung des Bundesbeschlusses über die Kontrolle von Blut, Blutprodukten und Transplantaten (22. März 1996) vom 8. Oktober 1999
	Bundesgesetz über die Transplantation von Organen, Geweben und Zellen (Transplantationsgesetz). Entwurf, Dezember 1999, mit einem erläuternden Bericht (http://www.admin.ch/ch/d/ff/2002/29.pdf (explanatory report) and http://www.admin.ch/ch/d/ff/2002/247.pdf (law)).
	Verordnung über die Kontrolle von Blut, Blutprodukten und Transplantaten (Blut-Kontrollverordnung). Änderung vom 23. Mai 2001

6. Summary and conclusions

In this chapter, the information presented in this report will be summarised by discussing the question how realistic it is that xenotransplantation can achieve its aims. The aims of xenotransplantation can only be achieved if the following prerequisites are fullfilled:

- availability of those organs which are in short supply
- equal access to xenotransplants for all patients in need of an organ
- xenotransplant function must be at least equivalent to allotransplant function

At present, it is

- an open question whether xenotransplantation will supply all required organs. It is more likely that only certain organs (e. g. hearts) can be provided through xenotransplantation, and that solutions for the shortage of other organs (e. g. liver, lung) are unlikely to come from xenotransplantation. This raises the questions
  - whether ressource allocation to xenotransplantation is justified if it only provides a partial solution to the organ shortage problem.
  - how ressources should be allocated between xenotransplantation and alternatives.
- clear that xenotransplantations will be at least as expensive as allotransplantations, and thus be a relatively expensive high tech option. At present, it is an open question whether and how equal access to allo- and xenotransplantation can be guaranteed, and what the consequences regarding a just ressource allocation within the national health care system and on supranational level are.
- most unlikely that xenotransplants will function as good as allotransplants within the foreseeable future. This is due to four unsolved scientific-technical problems (rejection, physiology, psychology, infection).

The state of the art in these areas can be summarized as follows:

- **Xenograft rejection** is more vigorous, complex and different from allograft rejection. By using organs from source animals which had been "humanized" (expression of human complement regulatory proteins), maximum life-supporting xenograft survival in non-human primates has been achieved for 78 days (kidney), 39 days (heart), and 8 days (liver). Overcoming additional rejection mechanisms requires the introduction of further genetic modifications into the source animals, cloning of source animals, intensive medical immunosuppression of the xenograft recipient, and probably also tolerance induction in the xenograft recipient.

- The knowledge base regarding **physiological aspects of xenotransplantation** is still very incomplete. Despite the limited knowledge, physiology most likely constitutes a significant stumbling block to the progress of xenotransplantation towards clinical trials. Crucial differences in the composition and viscosity of porcine and human blood suggest that the microperfusion of all xenogeneic organs will be severely compromised in the human recipient, leading to reduced blood flow, blood stasis and thrombosis, even in the absence of rejection. The assessment of other physiological (in)compatibilities is organ-specific. The xenotransplantation of porcine **hearts** appears to be the least susceptible to major physiological incompatibility problems, but lethal disrhythmias due to anatomical differences in the intrinsic innervation of the heart still have to be overcome. In **kidneys**, differences in the renal handling of creatinine, urea, and electrolytes such as calcium and phosphate require further research in long-term experiments. It is unlikely that xenografted **livers** will function properly in the human recipient which is due to the complexity of their metabolic, hormonal and regulatory functions. The xenotransplantation of **lungs** seems to be the least advanced of all solid organs, and it is likely that the postural change from the supine position in the donor pig to the upright position in the human recipient will significantly compromise the lung function.
- **Risk of infection**. Xenotransplantation bears the risk that xenograft recipients may be infected by known source animal pathogens, and that previously unknown pathogens may emerge which might be a health hazard to patients, contact persons and the general population. The risk of infection due to porcine endogenous retroviruses (PERV) has been extensively investigated in the last years. This group of viruses has been thoroughly characterised on the molecular level, and also their infection behaviour in vitro. Up to now, no evidence for PERV infection of humans in vivo has been obtained, but good in vivo animal models are still lacking to address this question further. Measures for the prevention and control of events of infection have been discussed and developed for PERVs and known pathogens present in pigs; they comprise the breeding and housing of specific pathogen free source animals, the development of highly sensitive and specific detection methods for the infectious agents, the implementation of monitoring measures which aim at early detection of any infection events and prevention of transmission, the development of drugs for the control of the infectious agents, or the development of vaccines. Appropriate regulations are being discussed on supranational and national levels. In recent years, establishing regulatory oversight and compliance with existing guidelines and standards has markedly reduced the risk of XTP-introduced infection – at least in several countries - compared to the unregulated situation in 1995. Altogether, these advances allow greater confidence in the reasonableness of proceeding with limited clinical trials, provided the trials are accompanied by appropriate safeguards and there is reasonable basis for expectation of benefit to the participants (Chapman 2003).
- In analogy to allotransplantation, it can be assumed that xenotransplantation may have **unintended impacts on mental state, identity and personality**. These effects are likely not directly due to effects of the xenograft, but due to patients' differences in their ability

to cope with the transplantation of an organ psychologically. In allotransplantation, the ease of coping is correlated with the recipients' type of "concept of one's own body".

To sum up, at the present state of the art, it is unlikely that a patient would benefit from solid organ xenotransplantation; a prolongation of life for several days without improvement of quality of life seems achievable. Therefore, a general consensus has emerged in the last years that at present the possible benefit does not outweigh individual and collective risks so that no solid organ xenotransplantation should be performed at present.

In the medium term, bridging the waiting time until an allotransplant becomes available seems possible, at least for hearts. But if xenografts can only be used as bridges to allotransplantation, it is likely that this form of xenotransplantation will aggravate the existing problems of human organ shortage and human organ allocation.

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Author: Bärbel Hüsing

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