Projektbericht

Research Report

Increasing Public Involvement in Debates on Ethical Questions of Xenotransplantation

Monitoring of International Developments in Xenotransplantation

Baseline Evaluation

Bärbel Hüsing

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Zwischenbericht

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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 preliminary results of the second working step. The information will be updated at the end of the XENO project and a revised, updated report on the international development will be prepared. This report 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.

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.

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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 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 from living donors: more than 90 % of the transplanted organs function one year after transplantation surgery, and 80 % still four years after surgery. The 4-year survival rate, taken as average of all types of organs, is 50 to 60 %. 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 four years after transplantation in the USA, 1987-1997

Transplanted organ	Share of surviving organs of all transplanted organs	
	after one year	after four years
Kidney (living donor)	92,3 %	80,8 %
Kidney (dead donor)	83,1 %	66,7 %
Heart	82,6 %	70,4 %
Lung	72,5 %	46,9 %
Heart-Lung	64,1 %	44,7 %
Liver	72,9 %	62,8 %
Pankreas	76,6 %	63,9 %
Small intestine*	59,2 %	35,0 %

* The survival rates of small intestine grafts refer to transplantations carried out in the period of 1990-1997

Source: Transplant Patient DataSource (2000, February 16). Richmond, VA: United Network for Organ Sharing. Retrieved January 2001 from World Wide Web: http://www.patients.unos.org/data.htm

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

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. 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. 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, more than 80 % of the transplanted organs survive longer than one year and more than 50 % longer than five years (table 3.4). However, most organs are lost during events of chronic rejection which cannot be controlled sufficiently in allotransplantation (figure 4.1).

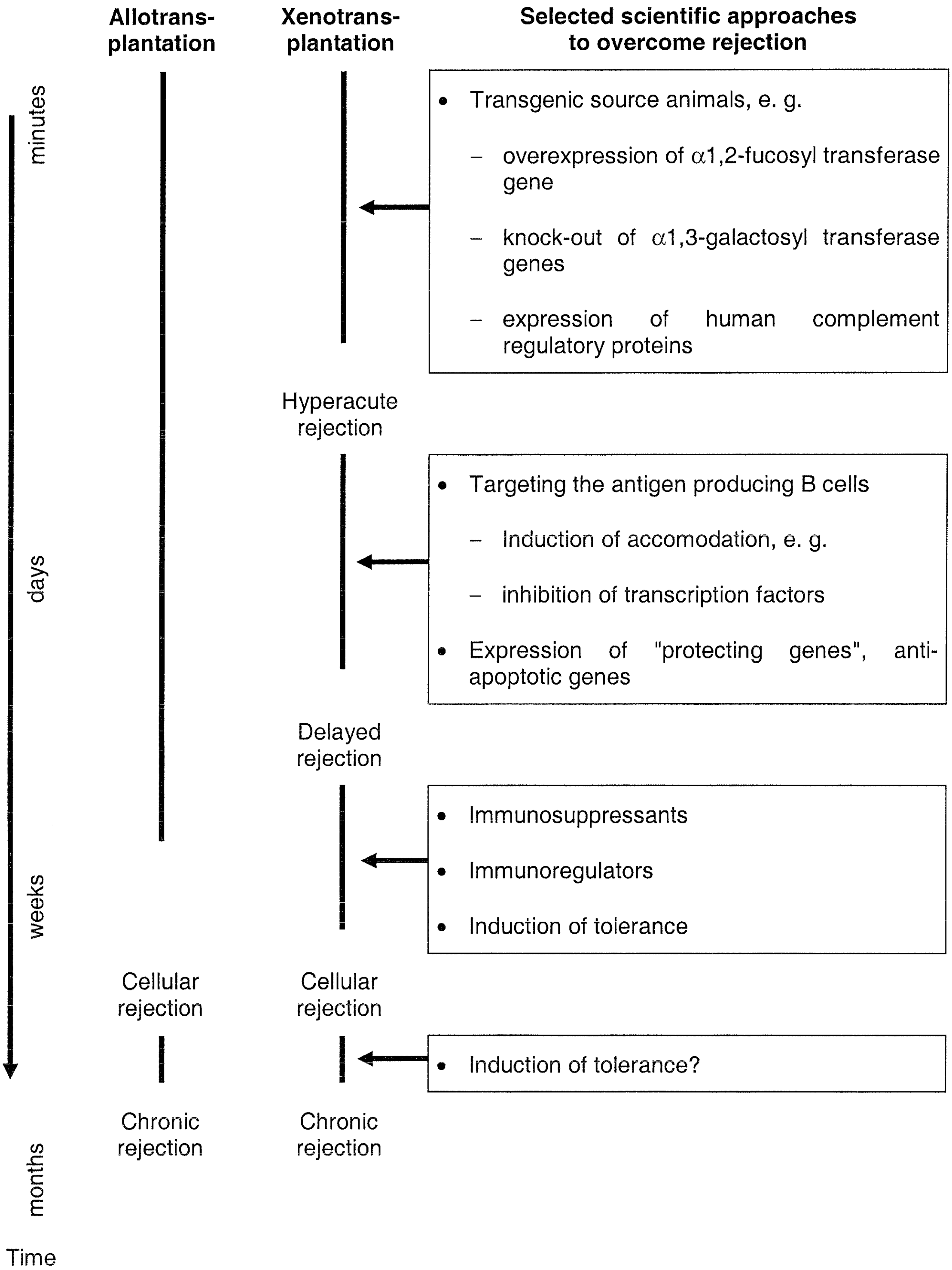
The immunological processes which underlie the rejection of xenografts are more complex and different from the rejection of allografts, and are less well understood (Cooper et al. 2002a; Cooper et al. 2002b). Figure 4.1 gives on overview of the different immunological processes involved. As can be seen 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.

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 an 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 hDAF-transgenic pigs are transplanted. 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. However, experiments are underway to test the combination of *different* control strategies, especially the combination of complement regulatory proteins with α1-3 galactosyltransferase. 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; Phelps et al. 2002; Platt 2002; Lai et al. 2002; see also chapter 4.5).
- 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 99 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 addition, in several cases 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.

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



Source: (De Wit 2001, p. 52), 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). 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. 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).

However, 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; Wekerle et al. 2001; Waldmann 1999; Sachs 1998; Greenstein et al. 1997; Sachs et al. 1995).

Table 4.1: Overview of survival times 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) Median	Max.	Remarks	Source
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	5	43	53		(Schmoeckel et al. 1999a)
		pig	Cynomolgus monkey	5	5 h	30		
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	7	13 (6-35)	35		(Zaidi et al. 1998)
		pig	Cynomolgus monkey	6	6.5 (0.3-30)	30		
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	9		68		(Loss et al. 2000)
		pig	Cynomolgus monkey	8		11		
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	234	102 animals 0-4 days 143 animals > 4 days			(Schuurman et al. 2002)
		pig	Cynomolgus monkey	11				
Kidney	yes	hDAF transgenic pig	Cynomolgus monkey	7		78	splenectomized, recombinant erythropoetin	(Cozzi et al. 2000)
		pig	Cynomolgus monkey	7				
		hDAF transgenic pig	Cynomolgus monkey	7			not splenectomized	
Liver	yes	hDAF transgenic pig	Baboon	2	min.: 4 days	8		(Ramirez et al. 2000)
		pig	Baboon	3		< 12 h		
Heart	no	hDAF transgenic pig	Cynomolgus monkey	8	5,1	5,25	no immunosuppress ion	(Cozzi et al. 1997)
		pig	Cynomolgus monkey	10	1,6	4,2		
Heart	no	hDAF transgenic pig	Cynomolgus monkey	10	40	62	with immunosuppress ion	
		pig	Cynomolgus monkey	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	hDAF transgenic pig	Cynomolgus monkey	57	41 animals 0-4 days			(Schuurman et al. 2002)
		pig	Cynomolgus monkey	8	24 animals > 4 days			
Heart	no	hDAF transgenic pig	Baboon	28	15 animals 0-4 days			(Schuurman et al. 2002)
		pig	Baboon	5	13 animals > 4 days			
Heart	yes	hDAF transgenic pig	Baboon	10	2,5	9		(Schmoeckel et al. 1998; Schmoeckel et al. 1999b)
Heart	yes	hDAF transgenic pig	Baboon	16	8 animals 0-4 days 8 animals > 4 days			(Schuurman et al. 2002)
Heart	yes	hDAF transgenic pig	Baboon	1	-	39		(Vial et al. 2000)

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 (Fishman 1994; Michaels et al. 1994; Chapman et al. 1995). 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, p. 58). Experts are confident, however, that most of these pathogens can be successfully excluded from herds of source animals if they are bred under specific pathogen free conditions. This, however, may be difficult for pathogens which are transmitted congenitally or through the germline (e. g. circoviruses, endogenous retroviruses etc.).
- *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. Especially 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).

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, p. 80-81).

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 Stoye 1998; de Wit 2001

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. Research has focussed on the group of porcine endogenous retroviruses (PERVs), but other virus groups (e. g. circoviruses) are also relevant (Rovira et al. 2002; Mueller et al. 2002; Mankertz 2002; Ehlers 2002). In the following paragraphs and in table 4.3, the present knowledge regarding porcine endogenous retroviruses is summarized.

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	(Le Tissier et al. 1997; Akiyoshi et al. 1998; 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	(Onions et al. 1998; Le Tissier et al. 1997; Martin et al. 1998; Wilson et al. 1998; Van Der Laan et al. 2000)
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	(Denner 1998; Denner 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 (Le Tissier et al. 1997; Akiyoshi et al. 1998; Martin et al. 1998). Research is underway to identify those PERV copies which are intact or defective, respectively (Bösch et al. 2000; Herring et al. 2001b; Niebert et al. 2002). 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 2-3 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).

Three classes of these PERVs are known which differ primarily in their envelope genes, use different receptors (Tönjes 1999) and therefore differ also their host range (Takeuchi et al. 1998; Wilson et al. 2000). 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 and certain blood cells) and therefore also in the organs and tissues which would be transplanted in clinical xenotransplantation (Onions et al. 1998; Le Tissier et al. 1997; Martin et al. 1998; Wilson et al. 1998; Van Der Laan et al. 2000). These PERVs can infect human cells (Patience et al. 1997; Specke et al. 2001a; Patience 2001; Czauderna et al. 2000) 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. 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; Denner 1999; Tacke et al. 2000).

However, there is no conclusive evidence whether transfer of PERVs to 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 received xenogenic transplants or had been treated by extracorporal perfusion of porcine organs or tissues were examined for signs of infection with PERVs. A discussion of these data can also be found in (Herring et al. 2001a). In addition, butchers who had blood-blood-contact with porcine blood were examined. In none of these cases, conclusive evidence for an infection with PERVs could be obtained. The limitations of the available samples for investigation are discussed in-depth in (Hüsing et al. 2001; Hüsing et al. 2000).

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 not in small animal models and non-human primates which received PERVs or porcine cells or organs during severe immunosuppression (Specke et al. 2001b; Denner et al. 2001b; Loss et al. 2001; Specke et al. 2002; Martin et al. 2002). However, non-human primates are not a suitable model to study possible PERV transmissions to humans because cells from non-human primates can only be infected, but no productive replication of the viruses takes place (Ritzhaupt et al. 2002).

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 (Weiss 1998; Takefman et al. 2002) have on the infectivity and adaptation of PERVs?
- 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 in peripheral blood mononuclear cells	(Patience et al. 1998a; Paradis et al. 1999)
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)
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 neural cells for therapy of Parkinson's disease	11		(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)
Extracorporal perfusion of transgenic pig livers (hCD55/hCD59)	2		(Levy et al. 2000)
Butchers with blood-blood contacts with porcine blood	?		(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 (Onions et al. 2000; Boneva et al. 2001)

- 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). Highly sensitive and specific detection methods for PERVS have been developed, and 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 (World Health Organization (WHO) 1998; OECD 2001; United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) 1999a; United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) 1999b; United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) 1998). Regulations are under development on supranational level (Council of Europe). A screening for drugs which could inhibit PERV replication has been carried out (Qari et al. 2001). 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 et al. 2002). 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. Futhermore, 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. 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). Although survival times of appr. one month have been achieved in the pig-to-baboon 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 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. 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 1998b; Platt 1998a). 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

Role of the animal	Consequences for the animal
Life saver Improver of quality of life	Death of source animal
Foreign body	Humanizing by genetic engineering/cloning
Pathogen source	pathogen-free by raising under SPF conditions, breeding, genetic engineering/ cloning
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.

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. This 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. Cowan 2000; Costa et al. 2002). 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 (Niemann et al. 2001). In 2000, the cloning of pigs by nuclear transfer of adult or fetal cells was reported (Onishi et al. 2000; Polejaeva et al. 2000; Betthauser 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 (Lai et al. 2002; Dai 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 (Kaiser 2002; Butler 2002; Frankish 2002). Meanwhile, both groups have also produced the first double knock-out pigs which were born in August 2002 (PPL Therapeutics 2002; Phelps et al. 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 results can be expected in 2003/2004.

In addition, 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). Using this line of miniature pigs for further genetic modification of source animals, the risk of infection with PERVs could be further reduced.

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 achieved by 2005.

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 do not outweigh 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. 2000):

- 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).

Although the risk-benefit assessment may come to more favourable results than for organ xenotransplantation so that clinical application of cellular xenotransplantation is not totally excluded at present (Hüsing et al. 2001), 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 (Archer et al. 2002; McKenzie et al. 2002; Collignon 2002; Valdes 2002; Dalton 2002; Valdes Gonzalez 2002; Anonymous 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).

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, p. 49-50). 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 pursue d 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

Disease	Type of cell/tissue/organ	Patients treated/planned	Country	Clinical trial phase	Results	Year	Study pursued further
Huntington	Cotransplantation of porcine fetal neurons and a mouse cell line (genetically modified, macrocapsules)	0/?	?	planning stage	not yet available	2001	?
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: (Taniguchi et al. 1997; Hüsing et al. 2001), with additions

5. 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 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 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 the individual and collective risks at present do not outweigh the possible benefit 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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Titel: Monitoring of International Developments in Xenotransplantation Baseline Evaluation

Projektbericht/Research Report

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