



FACULTY OF ARTS AND PHILOSOPHY

**PIG TALES, HUMAN CHIMERAS AND MAN-MADE PUBLIC
HEALTH HAZARDS**

AN ETHICAL ANALYSIS OF XENOTRANSPLANT BENEFITS AND RISKS

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{Title page: The illustration is an adaptation of the embryo drawings drawn by Ernst Haeckel in 1866 for his Recapitulation Theory}

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Table of contents

GENERAL INTRODUCTION

| | |
|---|---|
| 0. General introduction: definition, objective and scope..... | 1 |
| 0.1 Xenotransplantation definition | 1 |
| 0.2 Why xenotransplantation?..... | 2 |
| 0.3 Xenotransplantation ethics | 3 |
| 0.4 Research objectives and outline | 5 |
| References | 9 |

PART ONE: ESTABLISHING THE NEED FOR XENOTRANSPLANTATION

| | |
|---|----|
| 1 Transplantation medicine: evaluating its success..... | 11 |
| 1.1 The shortage of human organs: a 'formulaic' presentation | 12 |
| 1.2 Policies to augment the human donor pool: an overview..... | 13 |
| 1.2.1 Instrumental revisions of the 'dead donor rule' | 13 |
| 1.2.2 Augmenting the consent rate for cadaveric donation..... | 16 |
| 1.2.3 Optimising living donor utility | 20 |
| 1.2.4 Optimising cadaveric donor utility..... | 22 |
| 1.3 Transplantation: saving lives, the quality of life and health care expenses | 23 |
| References | 28 |
| 2 The ethics of organ allocation: frustrations in the face of finitude | 35 |
| 2.1 A right to transplantation? | 36 |
| 2.2 'Right' and 'wrong' in distributing the right to transplantation..... | 39 |
| 2.3 Earning points for moral behaviour..... | 40 |
| 2.3.1 Proposal outline | 41 |
| 2.3.2 Discussion | 44 |
| 2.4 Conclusion..... | 50 |
| References | 51 |
| 3 Organs galore: an overview of emerging alternatives to the donation model | 54 |
| 3.1 Not enough deaths to save the dying | 55 |
| 3.2 Maximizing living 'donation': commercialized transplantation | 56 |

| | |
|---|----|
| 3.2.1 Transplant tourism | 56 |
| 3.2.2 Arguments against commercialization..... | 57 |
| 3.2.3 Arguments in defence of commercialization | 58 |
| 3.2.4 Reality check: an illustration from Iran | 61 |
| 3.3 Artificial organs and support devices | 63 |
| 3.3.1 Artificial kidney and dialysis..... | 63 |
| 3.3.2 Liver support systems..... | 64 |
| 3.3.3 Lung replacement technology..... | 65 |
| 3.3.4 Total and partial heart replacements | 66 |
| 3.4 Bioengineered regeneration of tissues and organs..... | 67 |
| 3.4.1 Regenerative medicine: a look into the future | 67 |
| 3.4.2 Regenerative cells | 68 |
| 3.4.3 Therapeutic cloning | 70 |
| 3.4.4 Organogenesis..... | 70 |
| 3.4.5 Nonhuman animal growth environments..... | 72 |
| References | 73 |

PART TWO: XENOTRANSPLANTATION: PROBLEMS OF UNCERTAINTY

| | |
|---|-----|
| 4 Barriers to clinical xenotransplantation..... | 82 |
| 4.1 Standing the test of time | 83 |
| 4.2 Biological barriers to clinical xenotransplantation | 86 |
| 4.2.1 Immunological incompatibility..... | 86 |
| 4.2.2 Host or source animal manipulations | 89 |
| 4.2.3 Physiological incompatibility | 94 |
| 4.3 Restricting the emergence of xenogeneic infectious disease..... | 96 |
| 4.3.1 Contemporary relevance | 97 |
| 4.3.2 Xenozyoonosis | 98 |
| 4.3.3 Regulatory constraints to clinical applications..... | 100 |
| 4.4 Conclusion..... | 104 |
| References | 105 |

PART THREE: THE PIG - THE OTHER VICTIM?

| | |
|---|-----|
| 5 To the core of porcine matter: questioning the inherent immorality of producing transgenic pigs for xenotransplantation | 115 |
| 5.1 Introduction | 116 |

| | |
|--|-----|
| 5.2 Wrong for the sake of it..... | 117 |
| 5.2.1 Integrity arguments | 118 |
| 5.2.2 Intrinsic value arguments..... | 121 |
| 5.2.3 Sanctity of nature arguments | 124 |
| 5.3 Concluding remarks | 126 |
| References | 128 |
| 6 Use of pigs for xenotransplantation: the speciesism by proxy syndrome. | 132 |
| 6.1 Introduction: from primate to pig | 133 |
| 6.2 The prize animal | 135 |
| 6.3 Hogging moral status..... | 140 |
| 6.3.1 A clever pig extracts a deep root | 140 |
| 6.3.2 The moral relevance of suffering | 141 |
| 6.4 Life is what happens while you are busy making plans | 143 |
| 6.5 Conclusion..... | 147 |
| References | 148 |
| PART FOUR: PATIENT RISK/BENEFIT AND THE HARM PRINCIPLE | |
| 7 Eliminating the risk of secondary xenogeneic virus transfer..... | 153 |
| 7.1 Introduction | 154 |
| 7.2 Safety issues..... | 155 |
| 7.2.1 Moving ahead..... | 156 |
| 7.2.2 Proceeding with limited xenotransplantation trials and experiments involving human subjects..... | 156 |
| 7.3 A proposal for body donation in case of cortical brain death | 157 |
| 7.3.1 Living human subjects..... | 157 |
| 7.3.2 Living human bodies | 159 |
| 7.4 Discussion: the unbearable lightness of not-being..... | 163 |
| References | 169 |
| 8 Xenotransplantation and the harm principle: factoring out foreseen risk..... | 173 |
| 8.1 Dealing with the risk of a xenogeneic pandemic | 174 |
| 8.2 Do as you wish, but do not make a nuisance of yourself to others | 176 |
| 8.3 The ethics of man-made public health hazards..... | 179 |
| 8.3.1 Analogies | 179 |
| 8.3.2 Foreseeable risk..... | 181 |

| | |
|--|-----|
| 8.4 Foreseen risk and benefit | 183 |
| 8.4.1 The bad news | 183 |
| 8.4.2 The good news | 185 |
| 8.5 Implications of revised risk: an optimistic note | 188 |
| 8.5.1 Theoretical risk | 188 |
| 8.5.2 Natural and man-made pandemics | 189 |
| 8.6 Conclusion | 191 |
| References | 193 |

PART FIVE: HUMAN/ANIMAL INTERCHANGEABILITY: CONSEQUENCES FOR HUMAN AND PERSONAL IDENTITY

| | |
|---|-----|
| 9 Pig tales and human chimeras: socio-ethical issues related to xenograft recipient self-perception | 200 |
| 9.1 Introduction | 201 |
| 9.2 In search of the pig's tale: explanations for donor-mediated identity transformations | 203 |
| 9.2.1 Personal identity: it is all in your head | 204 |
| 9.2.2 Mad pig disease | 207 |
| 9.3 Recipient self-perception and the embodied self | 208 |
| 9.3.1 Biographical cells | 208 |
| 9.3.2 The embodied self | 209 |
| 9.3.3 Cultural category transgression | 213 |
| 9.4 Discussion: implications for xenotransplant recipients | 216 |
| References | 218 |
| 10 On the moral status of humanized chimeras and the concept of human dignity | 224 |
| 10.1 Introduction | 225 |
| 10.2 The moral worth of an ambiguous entity: a 'mind-bending' controversy | 226 |
| 10.3 Begging the question of human dignity | 228 |
| 10.4 The downfall of human uniqueness | 230 |
| 10.5 Defining humans as a set of mental and emotional adaptations | 233 |
| 10.6 Discussion: implications for the concept of dignity | 235 |
| References | 238 |

PART SIX: GENERAL DISCUSSION

| | |
|--|-----|
| 11 Summary, implications and recommendations | 243 |
| 11.1 Summary and implications | 244 |
| 11.1.1 Harm to non-persons | 245 |
| 11.1.2 Harm to persons | 246 |
| 11.1.3 Out of harm's way? | 250 |
| 11.2 Discussion | 253 |
| 11.2.1 Xenotransplant trials: a guinea pig race? | 254 |
| 11.2.2 The use of non-persons as experimental models: a body at will | 258 |
| 11.2.3 The 'greater good': critical notes | 263 |
| 11.3 Pursuing xenotransplant research: time to bring home the bacon? | 274 |
| References | 286 |

APPENDICES

| | |
|---|-----|
| 1 LEVY N. Respecting rights... to death | 295 |
| 2 CURRY S. Living PVS patients as legitimate research subjects: a response to Ravelingien <i>et al.</i> | 298 |
| 3 DRAPER H. PVS patients and research | 301 |
| 4 THOMPSON J. Relatives of the living dead: response to A. Ravelingien, F. Mortier, E. Mortier and J. Braeckman, 'Proceeding with clinical trials of animal to human organ transplantation' | 304 |
| 5. SPARROW R. Right of the living dead? Consent to experimental surgery in the event of cortical death | 307 |

GENERAL INTRODUCTION

0. General introduction: definition, objective and scope

Contemporary transplantation ethics is inextricably bound up with the ever-present scarcity of human cells, tissues and organs ('grafts') for transplantation. Due to the natural limits of the supply of vital organs and the expectation that the clinical needs for transplantation will continue to increase, there is no escaping tough trade-offs of the interests of some patients to receive a transplant against the interests of others. If we are to alleviate the suffering of the thousands of waiting list patients worldwide who currently cannot obtain a transplant in time, we must either root out the sources of disease or secure new remedies.

Researchers are developing new technologies that yield the outlook of virtually limitless supplies of transplantable grafts. One of the possibilities to augment the supply is the use of organs, cells and tissues from specially bred, genetically modified animals. That procedure, named xenotransplantation, is (or at least, certain applications of it are) predicted to become routine clinical practice in the near future.

It is not surprising that particularly that line of research is being pursued. In fact, some of the first grafts ever transplanted into humans were derived from animals. Nonetheless, the potential to sidestep scarcity by breeding an endless number of animals as sources of transplants for humans has generated ethical, cultural and regulatory questions that are entirely different from those that arose during the infancy of human-to-human transplantation. This dissertation has the aim to gain insight into the unique problems that emerge from this biotechnological procedure as well as to contribute to analyses and interpretations of the most troublesome inherent conflicts.

0.1 Xenotransplantation definition

The term 'xenotransplantation' (XTx) comes from the Greek word 'xenos' meaning 'foreign'. It stands for different technologies which intend to substitute inadequate organs, tissues or cells of one species for a live replacement taken from an individual of *another species*. Transplantations between individuals of the same species are called 'allotransplantations' (ATx). Although xenotransplantation could in principle involve any

cross-species transplants, current usage of the term primarily denotes the transferral of organs, tissues and cells from *pigs* to *humans*. United States Public Health Service policy has defined xenotransplantation as:

(...) any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.¹

This definition includes:

- the transplantation or implantation of any *solid organs or tissues* from an animal into a human patient to replace a diseased or damaged organ or tissue;
- procedures in which animal *cells* are transplanted or implanted into a human patient to compensate for the malfunctioning of the patient's own cells;
- a variety of procedures involving contact between human and animal cells, tissues or organs outside the body. *Ex vivo* contact may for instance consist of cross-circulating a patient's cells or fluids through an apparatus that consists of animal cells. Alternatively, the major blood vessels of a patient's malfunctioning kidney or liver may be connected to an animal organ placed outside the body. Also included in that definition is the culturing of human cells or tissue with animal cells in the laboratory in order to acquire a larger supply of human cells or tissue (e.g. human stem cell lines or skin cells grown on animal feeder layers).

Non-living animal products - such as pig heart valves, porcine insulin and vaccinations from animal sources or animal sera used for the culture of human cells - are not regarded as xenoproducts².

0.2 Why xenotransplantation?

The greatest promise of xenotransplantation lies in the expectation of attaining a reliable, long-term solution to bridge the gap between the supply of and the demand for transplantable organs³. Specially engineered pigs could provide suitable organs for practically all patients in need, including infants, for whom the organ shortage is the most devastating. Xenotransplantation could also provide an acceptable alternative for those individuals who do not accept human organ donation for ethical or cultural reasons⁴. Moreover, proponents of this biotechnology state that safe and effective xenotransplantation would annul many of the practical and emotional burdens related to

the long waiting times for an available cadaveric donor organ. With a source of grafts readily available, the transplantation procedure can be scheduled and prepared well in advance. Recipient pre-treatment can be conducted and the quality of organs can be screened in detail. The pathophysiological consequences of the interval between the declaration of death and the process of removing, cooling and preserving organs can be avoided. The source animals can be genetically engineered so as to optimize the functioning and to provide other potential advantages to the recipient. In addition, it has been argued that animal grafts may not be receptive to the human autoimmune diseases or viral infections that may have caused the organ failure in the first place or that can threaten graft survival after allotransplantation. Xenotransplantation may also widen the indications for transplantation. An abundance of animal-derived cells and tissues could potentially address currently unmet medical needs such as incurable neurological diseases, epilepsy, chronic intractable pain syndromes, paraplegia due to spinal cord lesions and insulin dependent diabetes.

0.3 Xenotransplantation ethics

Xenotransplantation has been fraught with controversy in light of the magnitude of both the hoped-for benefits and perceived potential harms. The major conflict to date is between ‘those who want to get it right’ and ‘those who want to get it right *now*’.

As indicated by Engels⁵, an ethical assessment of xenotransplantation must take into account both the individual level - where the expected benefits for the patient have to be weighed against the possibility of individual harm - and the possible collective harm xenotransplantation might cause. Given that the technology is fundamentally dependent on the use of animals, animal welfare and harm must also be assessed.

Like all experimental medical procedures, xenotransplantation applications bear a potential of harm. Most evidently, xenotransplantation involves a higher risk of organ rejection than allotransplantation due to the genetic distance (discordance) between pigs and humans. It also increases the risk of complications such as new infections and tumour formation. That challenges the medical-ethical requirement of ascertaining that the risks outweigh the expected (medical) benefit and that both sides of the balance can be adequately conveyed to patients as part of the informed consent requirement. What distinguishes xenotransplantation from other medical procedures, however, is that the

nature of some of the harms at stake undercuts the validity of agreement on the benefit/risk (im)balance between patient and physician only.

Unlike other fields of medical research, xenotransplantation involves the use of animals not only for pre-clinical experimentation, but also as the fundamental ingredient of the medical applications themselves. The question whether it is justifiable to use animals for 'spare parts' for humans has gained in import in a society that has become increasingly sensitive to the welfare of nonhuman animals. Unlike humans, animals have no choice in whether its organs or tissue are removed or not for human use. The animals are therefore referred to as 'source animals' rather than 'donors'. Xenotransplantation evokes objections towards the specific circumstances under which the source animals are born, raised and killed; circumstances that are said to compromise animal welfare and elicit significant suffering. To some, the use of animals as an end to human means is a denial of their right to life and renders them 'the other victim'⁶ of the organ shortage dilemma.

The most controversial issue from a societal standpoint, however, is the possibility that, in promoting individual benefit, xenotransplantation will also introduce a public health threat. Increasing concern has been expressed about the theoretical possibility that infectious agents from the source animal may be transmitted along with the xenograft and spread beyond the initial recipient to his or her close contacts and, at worse, to the community at large. It is well established - and topically illustrated by the recent outbreak of H5N1 Avian Influenza - that many of the infectious diseases that have emerged over the past decade can be traced back to animal-derived viruses, bacteria or prions that have passed onto or adapted in human hosts. Xenotransplantation appears to constitute a particularly pertinent health hazard. That is due to the fact that transplantation bypasses most of the patient's usual protective physical and immunological barriers. There is also a lack of knowledge about the behaviour of source animal-derived infectious agents in immunosuppressed humans.

The 'dual level' of risk constitutes a clash of two intuitively felt moral duties. By not pursuing xenotransplantation trials, we could be said to refrain from fully addressing the needs of waiting-list patients. By pursuing xenotransplantation trials, on the other hand, we could be helping some individuals at the cost of harming (possibly many) others. The question that arises is to what extent it is permissible for an individual to impose risks on others for his or her own benefit. The issue of just distribution of health burdens becomes

all the more intricate in recognition of the fact that viruses can hop borders and threaten populations that are unwilling or unable to participate in xenotransplantation medicine.

Still other factors may impede permissibility of xenotransplantation on the individual-societal level. Xenotransplantation abandons the concept of transplantation as an altruistic ‘gift’ and renders it a matter of patentable products that are readily available upon purchase. Furthermore, our cultural depiction of pigs may evoke religious constraints or emotional aversion, which can contribute to exceptional difficulties to adjust to the xenotransplant psychologically (both for the recipient and his or her social environment). Cultural resistance to xenotransplantation is also related to the fact that it involves the creation of ‘animal/human chimeras’, entities characterized by the side-by-side presence of both human and animal cells. The intermixing of biological material from different species, particularly from humans and nonhuman animals, evokes various concerns. The fact that the source animals are genetically engineered to express human proteins - a procedure that aims to counter the first stages of xenograft rejection by the human immune system - raises objections against interfering with the nature of the animal or against interfering with nature as a whole for that matter. The fact that a xenograft recipient can also be seen as a composite of animal and human material raises concerns about the effects both on the identity of the host and on societal and philosophical notions of ‘humanness’ and related concepts of moral worth.

0.4 Research objectives and outline

This dissertation intends to contribute to the broader debate of how to weigh the potential benefits of xenotransplantation against the costs that it may infer on the relevant agents at stake. Within that scope, special attention will be focussed on possible harms that arise uniquely or *predominantly* within the context of xenotransplantation. For that reason, not all of the implications of this biotechnology will be considered in detail. In particular, we will not engage in the debate on whether xenoproducts undermine the value of altruistic organ donation or not. That issue will be rather broadly addressed in our discussion of proposals to augment human donation by offering an incentive. In effect, it is not a unique concern when considering other replacement technologies such as artificial organs and regenerative medicine. For the same reason, the question whether it is justified to allocate health care resources to what some may call an ‘exotic’ form of treatment will be only briefly considered in the general discussion. The aim of the ethical analysis here is to

supplement the international literature on xenotransplantation ethics by indicating lacunas, inconsistencies or incompatibilities in considering the major stumbling blocks to accepting xenotransplantation as a viable alternative.

In PART ONE, we present three papers that indicate the *raison d'être* for xenotransplantation research. Chapter 1 sets out the magnitude of the human donor shortage and the development of medical and societal approaches to facilitate human donor procurement. This chapter also includes considerations of medical efficacy, cost-effectiveness and the comparative share of diseases treatable through transplantation in the most common causes of disability and death. Chapter 2 discusses what appears to be the core ethical controversy in the field of allotransplantation today: that some level of rationing is inescapable in light of the scarce commodity of donated grafts, leaving us to decide how best to allocate. Contention over what constitutes 'fair' selection has prompted various alternative suggestions to help resolve candidate ranking. Included are references to social parameters that have no direct medical relevance. We will consider in depth the proposal to resolve the issue of unfair allocation by granting priority to candidate recipients who are themselves registered as donors. Chapter 3 examines various alternative approaches that compete with xenotransplantation in the potential to acquire virtually limitless grafts for transplantation. The approaches include the commercialization of grafts from living providers, the development of artificial replacements and the use of stem cell technology to 'grow your own' grafts or to support failing tissues/organs. While those possibilities are attractive and promising, we demonstrate in which respect they are likely to fall short of providing a substantial pool of transplantable organs and tissues in the near future.

PART TWO provides a brief overview of the xenotransplantation experiments attempted in the past and the clinical trials that are being pursued to date. This chapter outlines the state of xenotransplantation science and indicates the main barriers to its use as a successful clinical therapy. The review will clarify that the major brake on clinical applications is related to the possibility that xenotransplantation may cause adverse effects to third parties not involved with the potential clinical benefits.

PART THREE is concerned with the animals used for humans' benefits. This section addresses concerns about both intrinsic and consequentialist aspects of utilizing genetically manipulated source pigs for human transplant purposes. Chapter 5 investigates the validity of claims that it is intrinsically wrong to produce 'humanized' pigs for

xenotransplantation and categorizes such claims into several clusters of arguments: (a) arguments that focus on the so-called integrity of the genome, the organism and the species; (b) arguments expressing the belief that animals have a good of their own; and (c) arguments questioning the technological interference with the natural order. This analysis allows us to limit the definition of ‘harm’ to the sentient interests of the individual animals. Given that the thwarting of the animals’ interests is an inevitable element of the purpose for which they are bred, a justification thereof is the subject of the next chapter. In particular, we question the arguments underlying the common rationale that it is more ethical to use one type of animal (the pig) rather than another (the nonhuman primate) and investigate the morally significant distinctions between their interests.

If it can be justified to use animals for xenotransplantation purposes, the question arises how to balance the patients’ autonomy and the rights of the broader public. The dual level of the virus risk is the subject of PART FOUR. The initial response to the awareness of the xenogeneic virus risk was a ‘precautionary’ approach, which voices the need to ‘look before you leap’ and ‘be safe rather than sorry’⁷. That position is increasingly being criticized as too risk-averse. Regulatory agencies across the globe are attempting to stipulate the appropriate conditions under which xenotransplantation can be conducted in the clinic while safeguarding public health. Their solutions depend heavily on the need to install long-term surveillance and monitoring schemes of xenograft recipients and, in some cases, their contacts and the health care and nonhuman animal care workers involved. Chapters 7 and 8 address the ethical and practical difficulties that arise from asking human trials subjects to consent to lifelong monitoring requirements. It is argued that some of those requirements contravene generally accepted ethical codes and rights regarding experimentation on humans and severely limit patients’ autonomy. It is also shown that current public health measures cannot warrant watertight protection of public health. In light of those considerations, both chapters offer a different perspective of how to respond to the unknown potential for public health harm. Chapter 7 is concerned with the possibility that the risks of virus transmission cannot be excluded through pre-clinical (animal) models and can only be addressed through clinical trials involving humans. An alternative means of overcoming the safety and ethical issues is suggested: willed body donation for scientific research in the case of permanent vegetative status. Chapter 8 reconsiders to what extent the public should be guaranteed protection from a xenotransplant-related health hazard. It is argued that the harm principle is not a moral absolute. In light of the increased optimism that the risk of xenogeneic viral infection is not as compelling as it was a decade ago, some level of public health threat would be

acceptable if the foreseeable aspects of the risk are accounted for and if the perception exists that the benefits are both substantive and attainable. Emphasis on the need to exclude foreseeable effects of xenogeneic virus transmission puts the ‘unique harm’ and accountability of this man-made technology into perspective and serves as a reminder of our duty to take ‘natural’ health hazards at least as seriously.

The FIFTH SECTION deals with the ways in which the technology to transgress the boundary between humans and nonhuman animals threatens socially determined notions of identity. Chapter 9 addresses the fear that human/animal interchangeability will, either directly or indirectly, affect the way in which the human recipient experiences or perceives him- or herself. We represent several interpretations of how xenografting may interfere with symbolic, socio-cultural notions of the self and contribute to an exceptional psychological struggle to incorporate the transplant. The tenth and last chapter considers the implications of the creation of human/animal chimeras on what it means to be human. Here, we interpret xenotransplantation more broadly to include human-to-animal chimeras. Increasingly, animals are being developed to express a substantial amount of human cells so as to serve as research models to enhance our understanding of the aetiology and progression of human disease and to test new treatments. It is particularly within this field that controversy arises as to where to mark the boundaries for ‘humanness’ and the particular dignity related to it. That setting offers a productive opportunity to test the notion of human dignity and to re-emphasize the grounds of moral worth as a matter of varying degree, dependent on the nature of the entity’s interests.

The FINAL PART sets the venue for a brief summary of the major standpoints taken in the papers, for a general discussion of the most contested aspects of our argumentation and for tracing out the major implications of our standpoints.

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PART ONE

ESTABLISHING THE NEED FOR XENOTRANSPLANTATION

1 Transplantation medicine: evaluating its success

Abstract

Ever since the success rate of transplantation substantially improved through a better understanding and manipulation of the process of inter-individual organ and tissue rejection, the demand for human grafts for transplantation has gradually outgrown the supply. In response to that shortage, all possible means to increase the rate of transplantations are being sought and considered. In this chapter, we will review the various policies to facilitate donor procurement which have been adopted or proposed worldwide since the advent of transplantation medicine. Amongst the measures meant to augment the transplantation rate, radical modifications of the 'dead donor rule' have been proposed, requirements of consent for donations have been liberalized and the utility of cadaveric and living donations has been optimized. We will also address common justifications underlying this trend in terms of medical efficacy, cost-effectiveness and the proportion of indications for transplantation in the most common causes of disability and death in developed regions.

1.1 The shortage of human organs: a “formulaic” presentation

A better understanding and manipulation of the process of inter-individual organ and tissue rejection has resulted in a substantial increase in the success of transplantation. The demand for human grafts for transplantation (i.e. 'allografts') has been outgrowing the supply ever since. Worldwide, organ procurement and donation networks indicate lengthening active transplant waiting lists and substantial death tolls, particularly for patients awaiting solid organ transplants of kidney, liver, heart, lung and pancreas.

Per 1 January 2006, according to Eurotransplant (the international procurement and allocation organisation that covers Austria, Belgium, Germany, Luxemburg, the Netherlands and Slovenia), 11,814 patients were enlisted as waiting for a kidney, 2,134 for a liver, 946 for a heart and 738 for lungs¹. During 2004, a total of 1,449 patients died while awaiting a transplant². On 18 January 2006 the United Network for Organ Sharing (UNOS) counted 90,628 waiting list patients across the US³. That number includes patients who are waiting for *multiple* organs. Between January and October 2005 a total of 23,511 solid organ transplants were conducted from 12,090 (both living and cadaveric) donors⁴. Again, the gap between supply and demand is most pertinent for kidneys: a 4 per cent annual increase in the number of transplanted kidneys cannot sufficiently compensate for the 11 per cent annual increase in demand⁵. As a result, people have to wait several years for a deceased donor kidney transplant⁶. In 2003 the US Organ Procurement and Transplantation Network (OPTN) reported a total of 7,147 deaths among the 114,442 patients on the waiting list (for all organs and on a national level)⁷. That amounts to an average of 19 to 20 deaths a day.

Those waiting list statistics may gravely underestimate the number of patients who actually require a transplant. For instance, in view of the scarcity of organs, a strict qualification of medical utility criteria is applied before a patient is considered eligible for the waiting list. Moreover, potential patients may not have infrastructural nor (in profit-based health care systems) financial access to waiting list submission. Although the World Health Organization estimates that worldwide 80,000 organ transplants and 1.5 million tissue transplants are conducted annually⁸, it is believed that this amounts to as little as 5 to 15 per cent of the number of transplants that would be carried out if the supply were unlimited⁹.

Basing the need for more transplants on statistical indications of demand/supply disparities is a criticisable approach. Joralemon argues that such a “formulaic presentation” misleadingly leads to the assumption that transplantation medicine is an “unquestionable good” that should be fully pursued¹⁰. This assumption, however, is not only inferred from waiting list statistics. The appraisal of the success of allotransplantation is reflected in the various policies that have been adopted or proposed worldwide since the advent of transplantation medicine to facilitate donor procurement.

1.2 Policies to augment the human donor pool: an overview

Amongst the measures meant to augment the transplantation rate, radical modifications of the ‘dead donor rule’ have been proposed, requirements of consent for donations have been eased and the utility of cadaveric and living donations has been optimized.

1.2.1 Instrumental revisions of the ‘dead donor rule’

The ‘dead donor rule’, the most primary ethical and legal rule on the subject of human transplantation, stipulates that life-sustaining grafts may only be procured from humans after death. Traditionally, the rule implied that retrieval of hearts, lungs, and livers from a potential donor was permissible only after establishment of irreversible cessation of spontaneous respiration and circulation. However, with cardiac arrest, body tissues are deprived of blood flow and oxygen supply, due to which potentially transplantable organs and tissues rapidly deteriorate, rendering them unsuitable for transplantation. The scarcity of suitable grafts has prompted several suggestions and decisions to modify the dead donor rule entirely or to interpret it more broadly.

Whole brain death

The need for cadaveric donors generated a redefinition of death itself, with a shift from cardio-pulmonary to brain function criteria of death. In January 1968 The Ad Hoc Committee to Examine the Definition of Brain Death identified reliable clinical criteria for the diagnosis of respiratory-dependent patients who have lost all brain functions¹¹. This group of patients had emerged from the development of intensive care medicine and life-support systems. The position came up that patients in those conditions have reached the

point at which they ought to be treated as dead rather than as beings in a clinical state in which further treatment is futile. It was argued that irreversible loss of all functions of the brain correlates with the irreversible loss of one's "personality, his conscious life, his uniqueness, his capacity for remembering, judging, reasoning, acting, enjoying, worrying, and so on."¹² The endorsement of the view that such a state constitutes death, is said to have served two purposes¹³. On the one hand, it aimed at alleviating the medical, technological and financial burdens posed by maintenance of those respiratory-dependent patients. It is nonetheless questionable whether these patients were a significant burden given the fact that they could be maintained for a mere maximum of hours or days only¹⁴. The main motivation for extending the criteria to declare someone dead, then, was to allow transplant surgeons to maintain artificial ventilation of a potential donor up to the point at which organ retrieval could be carried out. That limited the interval between the declaration of death and the process of removing, cooling, and preserving organs considerably.

Higher brain death

Shortly after the debate on the acceptability of using loss of brain functions as a criterion for death, a more complicated question emerged: precisely *which* brain functions are fundamental in terms of the death of the individual as a whole? One camp held on to the position that *all* brain function must be lost. A second camp took the view that it would be appropriate to treat an individual as dead even if some functions remain intact. Proponents of the latter view have argued for vital organ retrieval from anencephalic infants and patients in a permanent vegetative state, both conditions of 'higher brain death' in which brain stem functions (partially) remain, but either cerebral substance or function is irreversibly absent. The loss of higher brain functions renders the patient permanently unconscious and non-sentient up to the point at which cardiopulmonary and all brain functions cease to function as a matter of course. Several cases have been reported in which organs were harvested from an anencephalic baby^{15,16,17}, but in each case, organ retrieval was conducted after the establishment of natural whole brain or cardiopulmonary death. To date, no requests have been accepted to allow donation from anencephalic babies^{18,19,20} or patients in a permanent vegetative state^{21,22} as an exception to the dead donor rule.

Elective ventilation

Suggestions have also been made to use donors who are certain to die but have not yet met the criteria for either whole or higher brain death. In case of elective ventilation, ventilation is maintained in order to secure transplantable organs until brain death eventually does occur²³. Elective ventilation would allow to keep a person's heart and lungs operating in scenarios where patients have suffered severe, but not immediately lethal brain insult, and for whom death is imminent. This procedure runs counter to normal recommendations to let the patient die peacefully by withdrawing all treatment. It also challenges the common medical ethical norm, which gives patients the right to give or withhold consent to treatment, but which only applies to treatment intended to *benefit* the patient.

Death row organ donation

In the early 1990s a condemned prisoner in Georgia, US, offered to donate his organs as part of his death sentence and sued unsuccessfully for the denial of his request²⁴. Ever since, serious debate has been held about the permissibility of procuring vital organs from willing persons at the moment of their execution^{25,26}. Considering that capital punishment remains on the statute book in more than 100 countries worldwide, it is clear that such a decision could increase the availability of transplantable organs considerably. Although organs were obtained from guillotined prisoners in France in the 1950s, and US prisoners on life sentences were allowed to donate in the 1960s²⁷, death row organ donation is currently prohibited in the United States and West European countries. A statute permitting prisoners to donate organs was briefly enacted in Taiwan (from 1990-1994) and is currently still into force in Singapore (since 1972) and China (since 1984)²⁸. It is estimated that the Chinese procurement in line with 'Rules Concerning the Utilization of Corpses or Organs from the Corpses of Executed Prisoners' has resulted in the retrieval of up to 90 per cent of the nation's transplant kidneys. China has also been the subject of criticism due to indications that the organs obtained from such prisoners are 'sold', a practice which the Chinese government recently said it would ban²⁹.

Non-heartbeating donation

Due to the persistent organ shortage, retrieval of organs from persons declared dead on the basis of irreversible loss of heart function has been re-implemented. Cardiopulmonary

death remains a much more frequent cause of death than whole brain death. The University of Pittsburgh Medical Center proposed a non-heartbeating donor (NHBD) protocol in 1992³⁰. According to that proposal it would be allowed to take patients who have volunteered to become organ donors to the operating room before withdrawal of life support with the intention to retrieve organs as soon as the heart stops and death is pronounced. Various transplant centres have followed that lead. Initially only kidneys were deemed suitable due to the higher risk of problems related to the prolonged warm ischaemia (i.e. shortage of blood supply to the organ) before preservation³¹. To date, kidney, liver, and pancreas transplantations from controlled NHBDs appear to function well too, if the warm ischaemia time is less than 30-45 minutes and is followed by *in situ* perfusion cooling of the organs³².

Survival lottery

The most radical revision of the dead donor rule would consist in abandoning the requirement not to kill people altogether, in order to retrieve vital organs. In a famous 1975 paper 'Survival Lottery', John Harris developed an argument for arbitrarily killing persons to provide organs for others³³. His argument is based on the consideration that the benefits in terms of lives saved far outweigh the costs in terms of lives lost on the one hand, and on the assertion that there is no fundamental difference between a physician who kills directly and one who kills indirectly through failure to provide available life-saving medical procedures. Harris proposed a 'lottery' system (random selection) in which all citizens run equal risks of being sacrificed. Acceptance of this procedure would depend on the acknowledgement that everyone's individual chances of living are increased by that plan, as organ donation would no longer depend on the few people who volunteer to donate.

1.2.2 Augmenting the consent rate for cadaveric donation

Several efforts have been made to enhance the effectiveness of requests for consent to postmortem donation. Additionally, proposals have been put forward to circumvent the need for expressed prior consent altogether.

Expressed consent (opting in)

In most nations, organ donation depends on the generosity of donors and their autonomous decision to make a lifesaving ‘gift’. Their procurement protocols therefore emphasize the need of a prior valid expression of the deceased person’s wishes to donate. Nevertheless, with increasing indications that the number of individuals who express their consent during their lifetimes is insufficient, there has been much focus has on strategies to facilitate the donation process.

Required request

In most nations with opting-in legislation, including the US, consent may be requested from the next of kin in case prior expressed consent of the deceased is lacking. Nevertheless, various surveys estimate that only 40 to 60 per cent of the total potential donors in the US actually donate or have surrogates donate on their behalf and have their organs used³⁴. Attempts to maximize recovery of donors include the 1987 amendment of the Uniform Anatomical Gift Act that obliges hospitals and emergency personnel to develop procedures of ‘routine inquiry/required request’³⁵. This provision requires hospitals to ask patients, each time they are admitted, or their families, when the patient is dead, about the patient’s desire for organ donation. If the patient expresses the intent to donate his or her organs, that information is added to the patient’s record. Additionally, the Pennsylvania law Act 102 requires hospitals to call the regional organ procurement organisation regarding every patient’s death to determine the suitability of his or her organs for donation³⁶.

Improved communication

Many expressed consent legislations are faced with a well-known ambivalence between a widely shared positive attitude towards organ donation on the one hand, and resistance to act upon this attitude when the potential donor is a former loved one or the imagined dead self on the other³⁷. To address the unwillingness to consent between surviving relatives, North American procurement organisations now approach families in a more affirmative way, actively endorsing the presumption that people generally support postmortem donation, and that it is indeed the *right thing* to do³⁸. That ‘presumptive approach’ seemingly gives the family the opportunity to ‘opt-out’ rather than ‘in’. Internationally, focus has also been directed towards expanded training for those who

must ask for the consent³⁹. The lack of consent to organ donation has also prompted identification of subpopulations less likely to embrace organ donation. Studies indicate direct correlations between willingness to donate and prior family discussions on the subject, level of formal education, and the extent of accurate knowledge about organ donation/transplantation⁴⁰. Presumably, appropriate public exposure would provoke more family discussion and more frequent declaration of one's wishes to donate. It could also counterbalance psychological inhibitions to donation, such as the mistaken belief that one will receive less than adequate medical care if identified as a donor, and lack of skill in making decisions at highly stressful times⁴¹. Studies have shown that improvement measures in the whole donation process have resulted in an immediate overall increase of donation rates of up to 59 per cent after 1 year in 10 countries⁴².

Required response (mandated choice)

Under mandated choice, all competent adults would be obliged to decide on their willingness to donate organs upon their death⁴³. Suggestions have been made to request one's status as organ donor on tax returns, driver's license applications, or official identification cards, and to not accept those applications without an expressed decision⁴⁴. The choice would be binding - unless modified by a written directive at any time - and could not be overridden by the family unless that person has granted his or her family veto power. A variant of required response was tried out in the Netherlands in 1998 but was found to have a backfiring effect on the donation rate. Twelve million Dutch adults received a donor registration form in which they were asked to register which (if any) organs and tissues may be obtained in the case of brain death. Only four million people filled out the forms and sent them in, of whom 34 per cent registered an objection⁴⁵. Pilot studies of the mandated choice model in Virginia and Texas were not encouraging either⁴⁶.

Presumed consent (opting out)

At least thirteen European countries, some of which are leading organ procurement countries worldwide, operate under presumed consent legislation. Within such a system, an individual's wish to donate is presumed in the absence of an actual statement. Unless an individual 'opts out' by registering an explicit objection during his or her lifetime, the authorities can assume that he or she has permitted donation. The reasoning underlying implementations of 'presumed consent' is that people often do not express consent due to negligence or lack of knowledge about the process of consent, rather than fundamental

objection. The impact of changing to a presumed consent system on the donor procurement is in some cases quite compelling. Belgium, for instance, which passed the bill for presumed consent on 13 June 1986, obtained 37.4 donated kidneys per million in 1988, compared to 20 kidneys donated per million in 1985⁴⁷. Three years after the law was passed, Leuven saw its donor rate rise from 15 to 40 donors per year. Antwerp, which did not switch to presumed consent, maintained its previous levels.

Although consent is presumed in the lack of explicit individual objection, the surviving relatives retain the opportunity to oppose this (and actually do in approximately 15 per cent of potential brain dead donation⁴⁸). As such, many presumed consent systems encourage additional *expressed* consent to evade potential conflicts with family members. Since the launch of a public campaign on organ donation in June 2005, Belgium has witnessed a near doubling of the number of positive registrations (48,9 per cent)⁴⁹.

Conscription without consent

Suggestions have been made to surpass the need for consent altogether, on the basis of societal appropriation ('conscription'/'routine salvage') of cadaveric organs⁵⁰. Some states of the US have modified the Uniform Anatomical Gift Act to allow for 'tailored' routine salvaging. Under certain circumstances, organs may be procured when there is 'no known objection,' of the deceased individual, when there are at least symbolic indications of donor preference and if all attempts to reach and consult the family were unsuccessful⁵¹. While the routine salvaging of grafts from deceased individuals could dramatically increase the organ procurement rate, it is feared that it would damage public trust in the medical profession. This assumption lacks large-scale empirical support at this moment, although Spital conducted a modest telephone survey (n=1014) in continental US and found that 66 per cent of the respondents opposed organ conscription⁵².

Consent by incentive

Given the lack of altruistic donations, various ideas have emerged to boost the willingness of potential donors and/or surviving relatives to donate by way of an incentive. Among the many plans that have been outlined in keeping with this idea, a distinction can be made between incentives for living and cadaveric donation on the one hand, and between direct payment for the donated organs or other - more modest - incentives, on the other. Incentives for cadaveric donations may be directed both to the relatives at the time of a

donor's death, or to the actual donor during his or her lifetime. A 'future contract' could be established to commit a donor to the decision to donate after death, and would, for instance, consist in offering the prospective donors life insurance coverage, an income or estate tax incentive, free medical care, or priority for either him/herself or family members in case they themselves come to need transplants in the future. Alternatively, incentives for cadaveric donation for surviving relatives could include reimbursement of funeral expenses or a financial contribution to a chosen charitable organisation^{53,54,55}. In 1994 the Pennsylvania Funeral Benefits Pilot Program was proposed, intending to offer surviving donor relatives US \$3,000 for funeral expenses. (Please note that all references to dollars hereafter are US currency.) Due to opposition from the State Health Department, the program, which was finally launched eight years later, was severely altered and consisted of a mere \$300 benefit to pay for food and lodging costs incurred by a donor or a donor's family⁵⁶. More recently, US legislation introduced a proposal to offer living organ donors a one-time tax credit of up to \$5,000 to help to cover personal expenses⁵⁷. In comparison with the other suggested incentives, reimbursement of donor related expenses for living donors is well received and is explicitly allowed elsewhere (in particular in Belgium, Britain, France, Germany, Hong Kong, India, Japan, Luxembourg, the Netherlands, and the US)⁵⁸. Conversely, the direct purchase of organs from live donors has yet to be legalized (we will discuss this issue further in Chapter 3). The movement in favour of commercialization is nonetheless steadily gaining strength, partly as a response to the illegal traffic in organs⁵⁹. Direct financial gain proposals are generally focused on the idea to create a private or governmental supervisory agency that manages a market-driven procurement system of cadaveric or living donors. The distribution of organs, once collected, could be organized exactly as it is today⁶⁰, or by highest bid. Assessments indicate that a vendor program would be a cost-effective system for society⁶¹.

1.2.3 Optimising living donor utility

The first successful clinical organ allotransplant was conducted on 23 December 1954 under the direction of Joseph Murray. A kidney was transplanted between two identical twin brothers and resulted in nine-year recipient survival⁶². Thanks to the growing experience since, the results of transplants from living donors have improved and the practices of using unrelated donors and of transplanting segments of vital organs have increased.

Expanded pool of living donors

As recently as 1991 the World Health Organization recommended that living organ donation should be restricted to the use of genetically related donors in light of better matches and the related higher likelihood of graft survival⁶³. Developments in clinical immunosuppression have nonetheless allowed substantial improvements in the results of zero-antigen-matched living donor transplants. Kidneys from unrelated donors have achieved long-term survival rates (five-year graft survivals of 72 per cent), which are comparable to those for parent donor grafts⁶⁴. Moreover, owing to the advantages of elective performance of transplant procedures and reduced preservation times, living donor grafts result in better allograft function and long-term survival than cadaveric donor grafts. Consequently, kidney donations from individuals who are related to their recipients only through emotional bonds (friends and spouses) and, at some centres, even people who are not related to their recipients at all, are now considered acceptable⁶⁵. In the United States genetically unrelated individuals account for 33 per cent of the living donor pool⁶⁶. The prevalence of anonymous living kidney donation remains rare, but has nonetheless increased fourfold in the past 5 years⁶⁷. The pool of compatible living donors is further expanded through paired exchanges between two donor-recipient pairs. In those cases, there is a cross-donation from two willing living donors who are incompatible with their desired recipient but compatible with the other donor's desired recipient. From the same principle, living donors may also exchange their kidney for cadaveric organs⁶⁸.

Expanded pool of transplantable organs

Because of improvements in surgical techniques and immunosuppression regimens, segments of pancreas, intestine, liver, and lung are now also transplantable from living donors. The liver is among the few internal human organs capable of natural regeneration and can restore up to 75 per cent of lost tissue. Transplants of segments of the liver from live donors were initiated in 1994⁶⁹ and, while kidney donation remains by far the most frequent type of living organ donation, over 500 liver segment transplants have been conducted worldwide⁷⁰. The shortage of lung grafts from cadaveric donors has also prompted the development of a technique for performing lung lobe transplantation from living donors⁷¹. In most cases, the recipient receives bilateral lobar transplants from two different living donors. There has been no perioperative or long-term mortality following lobectomy for living lobar lung transplantation, although risk of death between 0.5 and 1 per cent has been quoted⁷². Living donor partial pancreas transplantation is a very new

procedure; the first transplant was conducted in January 2005⁷³. Even living *heart* donation is considered a possibility nowadays. In rare events, it can be determined that a deceased donor lung will function best in a recipient if transplanted in conjunction with the deceased donor heart. In that case, the prospective recipient's healthy heart is removed and becomes available for others on the transplant waiting list. Such living heart donation occurred recently, on 14 January 2006, from a four-month old domino transplant recipient⁷⁴.

1.2.4 Optimising cadaveric donor utility

Expanded criteria donors (marginal donors)

The crisis of organ shortage has compelled strategies to maximize donor utility beyond former contraindications related to donor age, comorbidities and systemic disease. It is believed that that approach can increase the current organ supply by 25 to 30 per cent⁷⁵. The use of such 'expanded criteria donors' generally implies a higher risk of suboptimal graft function and survival, although recent data support the policy to relieve restrictions related to donor age, diabetes, hypertension, or presence of multiple arteries, providing pre-transplant biopsy is acceptable. For liver transplantation - for which almost none of the most commonly used contraindications admitted in 1986 are valid today⁷⁶ - a similar level of function between livers of elderly donors and younger donors has been reported⁷⁷. Other studies have indicated that the long-term functioning of two marginal donor kidneys transplanted in one recipient is similar and in some cases even superior to that of a single ideal kidney^{78,79}. Transplants of grafts infected with viral hepatitis are also considered and may provide medical utility for recipients who have Hepatitis B induced liver disease, for instance, or for seronegative recipients in conjunction with appropriate antiviral preventive treatment.

Split liver transplantation

The liver's above mentioned capacity for natural regeneration also allows for two recipients to receive functioning liver grafts from one donor. An adult donor is divided in such a way that the left lateral liver graft can be transplanted into a small child and the right extended liver graft into an adult⁸⁰. One of the major advantages of this procedure is that it increases the pool of transplantable livers for small children, for whom the shortage

of organs is most extreme. Comparisons of the predicted lifetimes between whole liver transplantation for an adult recipient on the one hand and a split liver transplantation for both an adult and paediatric recipient on the other hand, suggest that split liver transplantation results in a net gain in life years. It also contributes to a larger number of successfully transplanted recipients using the existing supply of donor livers, even considering the higher rate of re-transplantation and death associated with these procedures⁸¹.

Organ reuse

The need to maximize donor utility has also induced the reuse of previously transplanted organs, such as a kidney or a liver, after early post-transplant death of the initial recipient. Recently, three case studies of liver re-transplants have been reported, demonstrating that livers may be safely reused as long as the graft was of good quality in the initial donor and was working well in the initial recipient. The authors note that 11 such re-transplants appear in the UNOS database from 1 October 1987 through 31 March 2004⁸². During this period, nine recipients were alive with a functioning graft. Previous case reports of liver reuse in Europe have also indicated reasonable survival rates⁸³.

1.3 Transplantation: saving lives, the quality of life and health care expenses

It is abundantly clear that all possible means to increase the rate of allotransplantations are being sought and considered. Against these efforts, however, critics call into question whether transplantation is currently the most attractive, or indeed, the only therapeutic option for the various diseases for which organ or tissue transplantation is now deployed. They argue for the need to prevent organ failure - rather than 'pick up the pieces' afterwards -, to take into account alternative therapies for organ failure, and to reallocate substantial financial, research, and institutional resources to less 'exotic' forms of health care, which will benefit a larger patient population. Critics also call into question the medical efficacy of transplantation in terms of quality of life and life years gained, by drawing attention to the adverse, sometimes life-threatening effects related to long-term post-transplant immunosuppression.

Improved prevention strategies for various diseases could indeed partly ease the transplant burden, at least in theory. For instance, pancreas or pancreatic islet cell transplants have been introduced as a viable therapy for diabetes. That disease is becoming alarmingly prevalent in western nations. With one in every adult having either Type 1 or 2 diabetes within the New York region, the problem has recently been identified as a genuine epidemic⁸⁴. Left untreated, Type 1 diabetes can result in major organ failure, amongst other complications, and currently accounts for more than 40 per cent of the cases of end stage kidney failure in the US⁸⁵. Nevertheless, although the growing incidence of diabetes parallels the increase in obesity, which is to a large extent avoidable, recent reports suggest that Type 1 - and perhaps one fifth of the cases of Type 2 diabetes as well - also has a genetic basis⁸⁶. Similarly, some organ pathologies can be congenitally acquired. Cancer, inflammation, infection or trauma are still other unpredictable and often misinterpreted causes of organ failure. Even in those cases in which prevention is appropriate, compliance of individuals to advice regarding healthier life styles cannot be controlled or enforced. Preventive measures on longer terms will also come too late for those who will need a transplant during the next decade(s)⁸⁷.

In terms of medical efficacy, organ allotransplantation has evolved to be the preferred treatment for severe failure of the heart, lungs, liver and kidneys⁸⁸. The use of immunosuppressants before the so-called cyclosporine era had a high death toll. Azathioprine, for instance, was administered until the early 1980s and related to an average mortality of 40 per cent at one year post-transplant⁸⁹. The subsequent introduction of cyclosporine in 1983 resulted in demonstrably improved outcomes in terms of kidney, liver and cardiac graft survival, life years and quality of life gained⁹⁰. Continued progress has been made in methods of immunosuppression, tissue typing, organ preservation, and surgical techniques⁹¹. The one-year survival of deceased donor kidney grafts is said to have improved from 82.1 +/- 0.5 per cent to 89.0 +/- 0.3 per cent between 1993 and 2002⁹², and the survival rates now exceed survival on dialysis. Cascalho and Platt note a three-year graft and function survival, almost without any form of rejection, for 77 per cent of cardiac transplants, 81 per cent of kidney transplants and 72 per cent of liver transplants⁹³. In a US study of all patients awaiting a deceased donor organ transplant - as enlisted in the Scientific Registry of Transplant Recipients - between 1995 and 2002, Schnitzler *et al.* found that per organ donor, 30.8 additional life years are obtained, distributed over an average 2.9 different solid organ transplant recipients⁹⁴. The use of all solid organs from a single donor provides 55.8 additional life years distributed over six

recipients. Liver, heart and kidney transplants contribute most to the overall life year gain.

The success achieved in transplant medicine has prompted the use of replacement therapies for non-vital disorders. As such, transplants of bone marrow, cornea, heart valve, skin, knee and various cellular transplants were introduced at the end of the twentieth century to contribute to the quality of life of many patients. In recent years the techniques to perform hand, limb and face transplants are being developed.

On a critical note, however, modern transplantation medicine is not without its drawbacks. In spite of improved short-term survival rates and a general triumph over acute rejection, results of five to ten years after transplantation still leave much to be desired. Recent data imply that long-term risk of graft loss - as a result of chronic tissue rejection and slow deterioration in function - may even have worsened⁹⁵. The incidence of secondary disease as a result of long-term immunosuppression is also considerable. Amongst the various complications are kidney failure, hypertension, diabetes, increased incidence of cancer and, most commonly, cardiovascular disease⁹⁶. It remains to be seen whether chronic rejection can be controlled. An exciting way ahead lies in research focused on developing immunological tolerance, a state in which a recipient lacks immune reactivity to the donor tissue but remains responsive to all other stimuli. Nevertheless, even if long-term graft loss cannot be prevented, a suboptimal solution to end stage organ disease may be acceptable in light of the life-and-death nature of the transplant.

Furthermore, transplantation medicine is indeed a costly affair, with substantial expenses related to donor organ retrieval, the transplant operation and long-term care of the transplant patient⁹⁷. Factoring in five years of follow-up charges, estimated transplant expenses range from an average of \$100,000⁹⁸ for a kidney transplant to \$3,000,000 for heart, heart-lung, and lung transplants and nearly \$400,000 for a liver transplant⁹⁹. Nonetheless, for most indications for which patients are currently put on the waiting list, transplantation is the most cost-effective therapy available. Many studies have established that successful renal transplantation (granted that graft survival and function is greater than 1.5 years) is more cost-effective than dialysis in the treatment of end stage renal failure^{100,101,102}. According to the Organization for Economic Co-operation and Development (OECD), kidney transplantation produces savings of 63 per cent¹⁰³. Pancreas transplantation is also more cost-effective compared to other treatment options for Type-1 diabetics with end stage renal disease¹⁰⁴. The cost-effectiveness of liver transplantation is less clear in

cases of alcoholic liver disease, but is in general less costly than the alternative of no transplantation at all¹⁰⁵. Additional support for cost-effectiveness is found in the economical advantages provided by re-entry of the transplant recipient into the employment market and in comparison to costs related to an enduring organ shortage¹⁰⁶.

A further argument in favour of allocating a substantial proportion of the health care budget to the field of transplantation lies in the fact that many of the diseases that are potentially treatable through transplantation are the most common causes of disability and death in developed countries.

| Developing Countries | # Deaths | Developed Countries | # Deaths |
|------------------------------------|-----------------|------------------------------------|-----------------|
| HIV/AIDS | 2 678 000 | Ischaemic heart disease | 3 512 000 |
| Lower respiratory infections | 2 643 000 | Cerebrovascular disease | 3 346 000 |
| Ischaemic heart disease | 2 484 000 | Chron. obstructive pulmon. disease | 1 829 000 |
| Diarrhoeal diseases | 1 793 000 | Lower respiratory infections | 1 180 000 |
| Cerebrovascular disease | 1 381 000 | Trachea/bronchus/lung cancers | 938 000 |
| Childhood diseases | 1 217 000 | Road traffic accidents | 669 000 |
| Malaria | 1 103 000 | Stomach cancer | 657 000 |
| Tuberculosis | 1 021 000 | Hypertensive heart disease | 635 000 |
| Chron. obstructive pulmon. Disease | 748 000 | Tuberculosis | 571 000 |
| Measles | 674 000 | Self-inflicted | 499 000 |

WHO: Leading Causes of Death in 2001¹⁰⁷

Contrary to the developing world, non-communicable disease by far constitutes the greatest cause of mortality within the industrialized world. US statistics specify that heart disease and malignant neoplasms (cancer) - were the nation's major causes of death in 2002, representing more than half of all deaths (respectively 28.5 and 22.8 per cent)¹⁰⁸. For advanced pulmonary and heart diseases, treatment with drugs or restorative surgery may not be possible. Cancer is in itself a leading cause of organ failure¹⁰⁹. Moreover, it has been suggested that future application of molecular diagnosis will be able to identify cancer in its earliest stages and pre-emptive transplantation would be a useful strategy to prevent the cancer from spreading¹¹⁰.

Parallel to medical advances and the aging of western nation populations, a continued lengthening of the list of diseases for which transplantation may be of benefit is expected. The number of patients who will succumb to end stage renal disease in the US is estimated to increase at an annual rate of 7-8 per cent¹¹¹. One person in five who reaches 65 years of age is expected to receive some form of organ replacement during his or her life span¹¹². Transplantation may also increasingly address non-organ failure related complications that arise as a result of an aging population, such as neurodegenerative disease. Indeed, neural transplantation has evolved over the last twenty years as a potentially curative approach for Parkinson's and Huntington's diseases as well as for demyelination, stroke and spinal cord injury. Particularly with regard to Parkinson's, the hopes of reversing the neurodegenerative processes are high. Although transplantation practices in those cases are still in an experimental stage, a review of all published results of patients with Parkinson's disease transplanted with human embryonic tissue found that most recipients improved significantly in motor skills and L-dopa administration, at least within the first 6 post-transplant months¹¹³. In a few patients, outstanding results have been achieved, with completely normalized dopamine production allowing them to quit L-dopa treatment completely¹¹⁴. Granted that islet allotransplantation is becoming a desired treatment for the majority of Type 1 diabetes patients, it is clear that the case for expanding the supply of such transplantable cells, as well as organs, should not be undervalued.

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2 The ethics of organ allocation: frustrations in the face of finitude¹

Adapted from: RAVELINGIEN A, KROM A. Earning points for moral behaviour. Organ allocation based on reciprocity. International Journal of Applied Philosophy 2005; 19(1): 73-83.

Abstract

Although not uncontested, the goal of organ and tissue replacement technology - as a means to delay individuals' "human finitude" - has been accommodated within a general frame of mind. Particularly for circumstances under which the only alternative for transplantation is death, there even appears to be a positive moral *duty* to pursue transplantation. For those who acknowledge a positive right to transplantation medicine, its purpose must not be rationed for health care economic savings. Unfortunately, some level of rationing is inescapable in light of the scarce commodity of donated grafts, particularly organs, leaving us to decide how best to allocate. Contention over what constitutes 'fair' selection has prompted various alternative suggestions to help resolve candidate ranking. Included are references to social parameters that have no direct medical relevance - such as age, deservingness or contribution to society. Recently, a Dutch philosopher, Govert den Hartogh, proposed a form of directed donation in which priority would be granted to candidate recipients who are themselves registered as donors. Given the prevalence of similar suggestions in international debates and the fact that den Hartogh's account provides one of the most well thought-out plans to manage the organ shortage crisis, we will, in what follows, consider the matter in some depth. We will suggest that steering organ allocation towards those who are themselves willing to donate organs is both an ineffective and a morally questionable means of attempting to improve procurement and allocation of transplantable organs. Suggestions to curb the eligibility to a life-saving transplant will nonetheless persist as long as there is a shortage of organs.

2.1 A right to transplantation?

It is undeniable that most of the aforementioned steps and suggestions to augment the transplant rate have been fraught with controversy in one way or another. Indeed, many of these controversies have helped shape - or, some would argue, directly brought forth - the content and focus of 'bioethics' as a distinct discipline². Since the advent of allotransplantation, Renée Fox and Judith Swazey (and many others after them) have explored the various ethical and social aspects which emerged from the replacement technology^{3,4,5}, many of which - as will be discussed from section three onwards - resurface in the context of xenotransplantation. Fox and Swazey were among the first in the field of transplantation to identify and comment upon complex problems of determining the death of a mechanically-assisted patient, of weighing the acceptability of immune rejection related risks and of deciding who shall live when both financial and graft sources are limited. They also analysed the various psychological and social experiences of all involved in the process of human-to-human 'spare part' donation. This included an anthropological inquiry into the moral obligation of humans to donate parts of their bodies to others, whether known or unknown, related or unrelated. They addressed the meaning and significance of the 'gift' of life-saving organ donation, a gift which is ultimately not repayable. They raised questions regarding the extent to which body replacement technology evokes recipient and societal views of the body as bionic, replaceable, adjustable.

After 40 years of firsthand research in the sociology and anthropology of organ replacement, these pioneers have recently recalled their involvement in the field, unconvinced by some of the assumptions on which organ transplantation is moving ahead:

(...) the "not-totally rational beliefs that transplantation is an unequivocally and unconditionally good way of sustaining lives, [and] that the more organs proffered, procured, and transplanted the better"; the "death is the enemy" to be "overcome" outlook that energizes these medical-surgical acts; and the hubris-ridden unwillingness to recognize and consent to our human finitude that this perspective implies.⁶

The quote serves here to demonstrate two realities. Firstly, it draws attention to ongoing cultural resistance to some of the implications of organ donation and transplantation. The ethical problems Fox and Swazey identified half a century ago remain of import and reappear in contemporary controversies surrounding the correlation between requirements

for consent for donation and the surviving interests of the dead, the imperative to view transplantation as a matter of voluntary gift, and defences of personal ownership over and commercialization of body parts. Cultural consensus is also lacking regarding one of the basic fundamentals of transplantation practice: the view that whole brain death entails the death of the individual. Japan, for instance, witnessed only fourteen cases of transplantation from brain dead donors up to 2001 due to society-wide rejection of this concept and the related notion that the essence of humans lies in self-consciousness and rationality⁷. By contrast, the negative feedback also exemplifies the extent to which the goal of organ (and tissue) replacement technology - as a means to delay individuals' "human finitude" - has been accommodated within a *general* frame of mind, at least within those parts of the world where it has become routine medicine. Particularly for circumstances under which the only alternative for transplantation is death, there even appears to be a positive moral *duty* to pursue transplantation further. The continuous efforts taken to increase human graft procurement suggest that, on a broad societal level, the most pertinent moral argument related to transplantation medicine is that precisely *more* should be done to facilitate transplant activities. In fact, various authors will support this positive duty even at the expense of other widely held ethical norms - such as the requirement for prior consent for postmortem donation. John Harris defends the latter argument in a rhetoric of common sense:

Why is there ever an obligation to rescue? Why do we have a health care system set up to remedy "unfortunate states of affairs"? I know that rhetorical questions are not arguments (...) but I am confident that simply asking the questions will show the moral poverty of any person, or any philosophy, that could even ask such a question with a straight face! I have to say that someone who does not see that the remediable suffering of others creates obligations is simply not a moral agent.⁸

Framing transplantation in terms of a moral duty evokes a sense of entitlement to transplantation, as part and parcel of the right to health care. In spite of the fact that the scope of any positive right to health care is necessarily limited by the many competing claims for the finite health care (budgetary) resources on which it rests, reasonable justifications of a claim to transplantation can be made from the perspective of maximized net aggregate benefit calculations and the maximin principle. As stated in the previous chapter, transplantation medicine promotes net aggregate welfare in terms of the population proportion that could potentially benefit from transplantation, as well as in terms of reduced overall health care costs. Alternatively, the maximin principle would suggest moral preference for those distributive decisions that maximize the wellbeing of the worst off, regardless of the net aggregate societal benefit on the whole. The

suggestion can be derived from applying John Rawls' theory of distributive justice of social goods, which impartially takes into account the interests of all members of the moral community. The impartiality is assured by what Rawls calls 'original position negotiations': imaginary discussions regarding the interests of various societal positions from behind a 'veil of ignorance' under the consideration that "no one knows his place in society, his class position or social status, nor does any one know his fortune on the distribution of natural assets and abilities, his intelligence, strength, and the like."⁹ Having omitted the individual, actual vantage point, the negotiators tend to make decisions that serve the best interests for all. Game theoretically, it is in everyone's interest that basic social resources and practices are reserved primarily for the least well off. In applying this general account of distributive justice to the distribution of health care resources, a case can be made that - at least within the developed world - the right to transplantation medicine outweighs entitlement to many other forms of health care. According to Norman Daniels, health care is a special case of rights to equality of opportunity¹⁰ (the equivalent, or condition even, of 'basic social goods') and should be distributed according to the extent to which a normal range of opportunities is protected. Disease and disability restrict an individual's range of opportunities, which would otherwise compromise his/her 'normal functioning'. The degree of lacking opportunities has an enormous impact on access to basic social practices and participation in all spheres of social life. Consequently, the most compelling claims for health care are for those therapies that maximize the opportunity of the least well off. Again, as indicated in the previous chapter - in terms of life-expectancy, quality of life, morbidity and mortality rates - it is clear that many forms of transplant medicine, particularly in the treatment of premature end stage organ failure, stand the test of maximizing the minimum 'opportunity' position.

For those who acknowledge a positive right to transplantation medicine, its purpose must not be rationed for health care economic savings. Unfortunately, some level of rationing is inescapable in light of the scarce commodity of organs for transplant, leaving us to decide how best to allocate. Which waiting list candidates are *most* entitled to a transplant? A precursor of the dilemma arose in traditional medical ethics in a different form, as the choice between saving one of two desperately ill patients when only one physician is available¹¹. In the current context, however, the predicament is a large-scale, daily matter, and has caused the public to view the transplant physicians as 'gatekeepers' of life¹².

2.2 'Right' and 'wrong' in distributing the right to transplantation

The argument could be made that each waiting list candidate should have equal opportunity for receiving a life-saving organ transplant, regardless of what his or her chances of benefiting from it are. However, giving all candidates equal chances at selection - without taking into account their various qualities of life, potential survival and strength of desire for a transplant - would go against our notions of medical efficiency and fairness¹³. Surveys have established that most transplant physicians would prefer allocation according to probability of good outcome¹⁴. This principle of 'medical utility' would favour allocation to those recipients who have the highest chance of benefiting and surviving from the transplant. This principle alone, however, is equally inadequate to fulfil a notion of fair and efficient distribution, since the interpretation of medical utility is not entirely dependent on medical facts¹⁵, but rather on how those facts are valued. It does not help us to choose between, for instance, a patient who has the greatest chance of graft survival; a patient who has the greatest predicted years of survival; a patient who would receive the greatest relief from suffering or morbidity; and yet another patient who would get the most personal satisfaction out of the transplant¹⁶. The present allocation formula of most policies compromises between considerations of medical utility and justice or fairness¹⁷, aiming for acceptable results in terms of patient survival and quality of life while also considering other factors, such as urgency of need (favouring those patients who are sickest and most likely to die) and waiting time.

Nevertheless, dispute over the relative weight of these factors remains. Contention over what constitutes 'fair' selection has prompted various alternative suggestions to help resolve candidate ranking. Included are references to social parameters that have no direct medical relevance - such as age, deservingness or contribution to society. Historically, elderly patients were not admitted to the waiting list under the presumption that younger candidates would obtain greater benefit¹⁸. In light of improved results, however, the controversy has shifted to the *moral* question whether elderly persons or repeat transplant recipients deserve an equal shot at an organ in comparison to young patients or patients who have not yet been transplanted¹⁹. Psychosocial or lifestyle criteria have also come under scrutiny. Suggestions have been made to exclude HIV-patients²⁰, criminals²¹, mentally incompetent patients²² and patients who require a transplant as a result of alcoholic liver disease (ALD)²³ from the waiting list. An alternative means of rationing the scarce 'goods' is by offering candidate donors the opportunity to designate the selection criteria for a future donation themselves. So-called directed donations -

which restrict the allocation to a particular person, institution, ethnic group or age category²⁴ - have to some extent been introduced in the past. In 2002, for instance, California State Senator Jeff Denham introduced legislation that allowed donors to debar allocation to prisoners²⁵. The United Network for Organ Sharing (UNOS) has formally rejected directed donations, claiming that it is discriminatory and threatens to undermine the whole logic behind the anonymity-based allocation process.

Directed donation raises interesting questions. For instance, the argument has been made that, despite it being discriminatory, it is better to permit directed donation than obtain no donation at all. By prohibiting this form of donation, the organs will go to waste and be of benefit to no one. Still a different argument can be made in defence of directed donation to certain racial groups. Although minority ethnic populations in the United States have an increased risk of developing end stage renal disease compared to whites, data indicate that white dialysis patients have more than double the chances of receiving a kidney transplant than black patients²⁶. This is in part due to profound racial differences in antigen expression and the fact that black individuals have less well-defined HLA antigenic specificities than do white patients. Directed donation to black patients could thus be defended as a means to lessen the gap in cross-racial antigen matching.

The debate surrounding the role of social criteria in the selection of candidate recipients is far from resolved and will remain an intrinsic aspect of the organ scarcity. Recently, a Dutch philosopher, Govert den Hartogh, proposed a form of directed donation in which priority would be granted to candidate recipients who are themselves registered as donors. In the opinion of den Hartogh, the procurement and allocation of donor organs should be seen as a system of reciprocity and not of goodwill and voluntary altruism. Given the prevalence of similar suggestions in international debates²⁷ and the fact that den Hartogh's account provides one of the most well thought-out plans to manage the organ shortage crisis, it is expedient to consider the matter in some depth.

2.3 Earning points for moral behaviour

In its own effort to ethically reduce the organ shortage, the Netherlands established the required consent law (opting-in) in 1998, emphasizing the need of explicit consent to donation by the potential donor or - if lacking - the next of kin. The rate of heartbeating cadaveric organ donations has nevertheless reached a disquieting plateau during the past

years. A recent increase in both living and non-heartbeating donations can only partly compensate for the widening gap between supply and demand. A comparative study with several Western European and other countries reveals that, among those Western European countries, the Netherlands is ranked third lowest in numbers of cadaveric organ donors per million inhabitants. With 12.3 effectuated donations per million inhabitants in 2001, the Netherlands is unable to meet the need for donor organs²⁸. Approximately 20 per cent of the adult Dutch population is registered as organ donor²⁹. Of the cases in which the will of the deceased is unknown and the decision is left to the next of kin - still the biggest source of donor organs - the family refuses in roughly 60 per cent of the cases. The family refuses even in 6 to 10 per cent of the cases where the deceased was registered as donor³⁰. In addition, when the potential donor is not listed in the donor registry, potential donor organs are wasted, as the family is often not even asked for permission³¹. It is within the context of this relatively low donation rate that Govert den Hartogh, Professor of Ethics at Amsterdam University, suggests that the practice of organ donation should be structured in a radically different way. In his study 'Gift or contribution?' he defends a change to a type of presumed consent system in which organ donation is seen as fulfilling a duty to contribute in a reciprocal relationship.

2.3.1 Proposal outline

According to den Hartogh, the current opting-in system must be replaced by an opting-out system, which he trusts will be more profitable. Within such a system - also known as 'presumed consent' - everyone is in principle regarded as a potential donor, unless the individual registered an explicit objection during his or her lifetime. Nevertheless, presuming consent in case of non-registration is still subject to doubt and leaves insuperable room for inappropriate family objections. Surviving relatives may be inclined to take non-registration as a sign of implicit objection and withhold their consent as a consequence, thereby negatively influencing transplantation rates. It is therefore important to anticipate ambivalent situations and to encourage people as much as possible to *register* their will to donate as well. Den Hartogh proposes to give those who have explicitly registered as organ donors, priority in receiving an organ should they ever need one. Such a priority position for registered donors could be guaranteed, he thinks, by granting them 'bonus points' if they are ever on the waiting list. Accordingly, donors would have better chances of receiving an organ if they were ever to need a transplant themselves.

The specific outline of den Hartogh's proposal draws on an analysis of what he believes to be major false preconceptions within Dutch donation and procurement processes. He believes that the apparent Dutch preference for the opting-in system is based on a mistaken focus on the interests that are to be protected by the demand for express consent. The argumentations in favour of consent emphasize the need to protect the right to self-determination and bodily integrity. In the opinion of the author, these interests become drastically reduced after death. As for self-determination, after death the only decisions that remain in practice relate to the type of donation (donating your organs for transplantation or donating your body to science) and the type of funeral. Even this self-determination is violated in view of the voice that the family members are still given in the matter. Accordingly, violations of bodily integrity lose much of their relevance after death and must be weighed against the overriding goal, which in this case is the more urgent need of third parties (the potential organ recipients). Moreover, the emphasis on self-determination and autonomy is inconsistent. If the right to determine what happens to your body is in fact so important, why is it that others, most often the family, can take over or even veto that right once you have passed away?

Furthermore, the current donation model is based on the false idea that organ donation is ultimately a *donation*, a voluntarily gift that is in no way obliging. According to den Hartogh, there is no question of 'non-commitment' in the realm of organ donation. Thoughts on both the 'Samaritan duty' to help a person in serious need and the 'duty of fairness' lead him to determine that organ donation is in fact a matter of fulfilling one's duty to help and contribute. It is through this insight only that we can thwart the 'free rider' who takes advantage of the fact that it is in everyone's interest that donor organs should be available, but in nobody's *direct* interest that his or her own organs are made available.

The Samaritan duty - the 'duty of easy rescue' - stipulates that you should help a person a) if he or she is in serious need; b) provided such action does not involve too high a cost to you; and c) provided you are in a unique position to offer help. The Samaritan duty would for instance apply if you were a coincidental passer-by who witnesses a child drowning. Provided that you can swim, and the cost of rescuing the child would be nothing more than a set of wet clothes, it is generally regarded a duty - in some countries legally mandatory - to help that child from drowning. Den Hartogh argues that the same goes for cadaveric organ donation. According to him, it is clear that the patients on the waiting list are in

serious need. The possible costs of postmortem organ donation are outweighed by the benefits to the patient. The organs are of no use to you after death, but can save another's life. As for the latter criterion, a donor is not literally in a unique position to offer help to the patient in need. In principle, anyone can be a donor. Nevertheless, a 'one-to-one' relationship can be *formed* when - with the help of a certain amount of coordination - the donor's organs are allocated to the first suitable person on the waiting list.

With 'the principle of fairness', den Hartogh turns to a second duty. Instead of supporting the notions of solidarity and charity, the author uses the 'principle of fairness' to indicate an obligation to contribute to what can become a system of *mutually assured help*. The principle of fairness implies that, in an undertaking offering reciprocal benefits to all parties involved, those who recognize these benefits have an obligation to make an honest contribution and not to take unfair advantage of other people's contributions. Organ donation, in the author's view, comes down to developing a common asset (the 'organ pool'), which is created on the basis of a collective effort (the collection of individual donations). The benefits of the contribution counterbalance the costs and are potentially relevant to everyone. In this case, since in principle anyone may at some time need a transplant, it is certainly in everyone's interest to be able to draw upon the available organ pool. According to den Hartogh, a person who objects to organ donation thereby indicates that he or she opposes the common asset that it produces. Hence, at least *in principle*, this person has no claim to an organ. Everyone must be given the opportunity both to live and to die in accordance with his or her own beliefs. It is ultimately inconsistent to refuse to consent to donation but at the same time think it fair to still potentially receive a donor organ.

Den Hartogh cannot guarantee that implementation of his proposal would substantially resolve the allocation problem, but he is reassured that it would not in any case work to anyone's disadvantage. Subsequently, he explains that awarding registered donors a *priority* position does not imply that those who have not registered or have objected are completely excluded from allocation. They are simply subordinated to registered donors. Although it would be in accordance with the fairness principle that a person should take responsibility for the choice he/she made not to donate, den Hartogh feels that offering no prospect of transplantation would elicit the counterargument that everyone has a right to lifesaving help. Moreover, den Hartogh acknowledges that there may still be people who wish to register as donors on a truly altruistic basis, preferring to direct their donation

unconditionally to anyone in need, rather than limit it to other registered donors. Therefore, he introduces the option of 'free' donation (in contrast to a 'restricted' donation). If a donor specifically chooses this option, then the bonus points would not be taken into account in allocating his/her organs. This is also the case with donors made available by family consent, in case the donor was not registered.

The bonus point system could easily be implemented into the currently used point allocation systems. As points are allocated on the basis of, for instance, waiting time, geographical distance between donor and candidate recipient, and the supply demand of donations in the member state concerned, extra points could also be allocated on the basis of donor registration.

2.3.2 Discussion

Den Hartogh's proposal needs to be situated within the growing realization that voluntary gifts alone cannot provide a sufficient number of donor organs. The adaptations to the 1998 Dutch organ law that he is suggesting are far-reaching, but touch upon some of the most current controversies in transplantation ethics. The idea of viewing organ donation as an undertaking involving mutual benefit rather than as a matter of charity is not new. It was suggested at the time of birth of the science of organ transplantation - ten days after the first heart transplant in 1967. At that time, Joshua Lederberg argued that organs should by preference go to those who themselves are prepared to donate³². The same notion has led to the establishment of the United States based 'Life Sharers', a growing yet unofficial donor network founded on the premise that one must first be prepared to give before one can receive³³. The members of Life Sharers consent to postmortem organ donation on the condition that other group members have first claim to the organs and tissues. If no suitable recipient is found within the group, then the organs can be allotted to non-members. Ultimately, of course, a claim on reciprocity is the basis of various suggestions (and practices) on financial compensation for donors or donor's families.

The fact that den Hartogh abandons the concept of donation as a 'gift' does not in itself constitute a problem, nor does it necessarily diminish the moral significance of the donating process. Indeed, the argument is increasingly being heard that organ donation does not need to be linked to altruism. In any case, a so-called altruistic donation does not preclude self-interest. Consider, for example, the need to give meaning to one's own death

or to that of a fellow human being. Nevertheless, this specific idea of giving donors bonus points for their moral behaviour gives rise to several difficulties. This is especially the case when addressing the two questions that are a pertinent part of assessing initiatives to boost donation: (1) how effective will the initiative be; and (2) how should it be assessed morally?

What dreams are made of

We identify three major concerns that throw doubt upon the likelihood that the reciprocity system as presented by den Hartogh will significantly increase the donor pool.

Our first concern has to do with the content of the reciprocity. If den Hartogh wants people to register their will to donate within a presumed consent system, he does need to give them some type of 'incentive'. The strength of a presumed consent system lies precisely in the fact that consent is given by *not* registering. Although the type of incentive den Hartogh offers registered donors - the guarantee of a certain priority arrangement on the waiting list - is practically attainable, it is worth questioning whether it will be sufficiently rewarding to motivate people to donate and if it will actually benefit donors fundamentally. It is difficult to anticipate the impact a donor bonus point would have in relation to the other allocation points taken into account. Even granted that such a bonus point would make a significant difference on the waiting list, the promised 'priority position' is still dependent on other factors, such as the number of other registered donors on the waiting list. It is paradoxical that the more registered donors there are, the less advantage an individual gains by registering. It is conceivable that such unclear benefit diminishes the appeal of positive registration, and of the entire proposal for that matter.

Our second concern has to do with den Hartogh's expectations related to a change of procurement system. While he acknowledges that other practical steps are required in order to increase the donation rate, such as donor education and donor counselling, great focus of his proposal is on the need to step away from the opting-in system. However, we are not convinced of the need to attribute that much influence to the type of procurement system with regard to the donation rate, as this remains a matter of debate. A hasty comparison between the top donating countries would indeed allow for attributing the difference to the procurement systems used: Spain, Austria, Belgium and Portugal all have a presumed consent system. However, while it is true that, between 1995 and 2002, the Dutch number of effectuated donors decreased by 11 per cent³⁴, other countries -including

those with an opting-out system- have also witnessed a decline of the number of donors in the past years. Moreover, while the refusal rate of Holland is relatively high (60 per cent) compared to that of Spain (opting-out, 22 per cent), low refusal rates are also possible in an opting-in system (see for instance the UK, 30 per cent). Sweden has an opt-out law but at the same time obtains a donation rate that is lower than that of the UK, which does not. In fact, implementation of presumed consent in Sweden did not have any visible effect on the number of donors. Also, within the opting-in system, the number of cadaveric organ donors in the Netherlands did increase from 202 in 2002 up to 222 in 2003³⁵. With this increase of 10 per cent Holland is almost back at the level of 1995 (228). Recent research also suggests that, while the donor potential of the Netherlands is currently much lower than that of Belgium, the donor efficiency -the total number of organs actually procured in relation to the donor potential- is very similar (respectively 6,8 and 6,7)³⁶.

All these findings suggest that it is too easy to think of a one-to-one relation between high refusal rates and opting-in (or between low refusal rates and opting-out). While in general terms presumed consent is much more productive than expressed consent, the success of a procurement organization is also highly dependent on other factors. It is known, for instance, that in Spain ten strategies are used to remove the objections of the relatives. Those strategies are not conceptually linked to the opting-out system and can in principle be applied in the setting of an opting-in system as well. In fact, the success of the Spanish model was not a direct result of the implementation of presumed consent, but rather due to the establishment of the National Transplant Organization in 1989³⁷. Many have voiced the opinion that it is not so much the procurement system, but rather the effective approach to surviving relatives and efficient donor recognition that are of paramount importance. The importance of donor recognition and routine request for donation is well illustrated by the results of 'Gift of Life', a North American organ procurement organisation covering a population of more than 9.8 million (residents of parts of New Jersey and Pennsylvania, and all of the state of Delaware). Since 1994 the number of donations within the Gift of Life region has grown by 75 per cent, as compared to a national increase of only 19.6 per cent over the same period³⁸. This remarkable increase is thought to be due to three measures that were introduced by the Pennsylvania Act 102 in 1994: routine referral of every dying person, donor registration upon obtaining one's driver's license, and ongoing awareness-raising campaigns aimed at the general public. The introduction of these simple measures has had an enormous impact. During the past five to six years, better results have been achieved within the Gift of Life opting-in system than in

the much praised Spanish model. In 2001, for example, Spain had 32.5 postmortem organ donations per million inhabitants; this figure was 36.4 for Gift of Life in the same year³⁹.

A last concern with regard to the effectiveness of den Hartogh's proposal is most directly problematic to the author: the public rejects his proposal. The Rathenau Institute conducted a public survey to examine the opinion of the Dutch population on different legal organ procurement systems -including the one outlined by den Hartogh. The survey clearly indicates that the majority of the Dutch population takes offence at the idea of organ donation in terms of reciprocity, even if such a system were to produce an increase of 20 per cent in donor organs⁴⁰. These results go very much against den Hartogh's interesting game theoretical explanation for the paradox that nearly everyone has a positive attitude towards organ donation, while at the same time only few people are willing to donate their organs (in the Netherlands one out of every five adults). What is keeping them from registering as a donor is the fear of being exploited, according to den Hartogh. They are afraid that their organs might go to a non-donor and that there will be no organ available should they themselves ever need one. The survey showed, however, that the different procurement systems did nothing to change the willingness to donate, only the willingness to register the willingness to donate.

The 'good', the 'bad', and the outcast

The negative results of the public survey suggest that there is something morally or at least emotionally troublesome about reciprocity within the donation setting. This comes as a surprise when we think of common situations in which many people feel that they are obliged to respond in kind to those who are benevolent, but that, on the other hand, they owe nothing to profiteers. This 'it's your own fault' reasoning implies that individuals themselves are at fault and should take responsibility for their choices. Why would the role of personal responsibility not apply when the choices come down to being eligible for an organ or not? This is essentially an ethical criterion. While the selection of candidate recipients is largely based on objective reasons in light of medical success, points are also allocated on the basis of various moral criteria. Extra points will generally be given, for instance, for long waiting times and if the waiting list patient is a minor or if he or she has been a living donor⁴¹.

The emphasis on personal responsibility within the practice of medicine is nevertheless a new and still very controversial matter of debate since responsibility is for the most part

not taken into account in relation to a health disorder. The 'It's your own fault' reasoning is not applied when, for example, someone is brought into the Emergency Room who has had an accident under the influence of alcohol. We would find such a rigid moralistic standard inappropriate in such a situation. Moreover, even though there is disagreement within the organ transplant debate as to whether a smoker or an alcoholic has just as much right to an organ as someone who does not smoke or drink, the question of blame is not consequently raised. Other causes of organ disorders that could just as easily be included in the debate on personal responsibility - such as heart and vascular diseases caused by stressful lifestyle and improper diet; and kidney failure caused by failure to maintain blood pressure⁴² - are not brought into the discussion. In such situations one could nevertheless also argue that 'you chose yourself for the behaviour that involved a predictable risk of ending up in trouble,'⁴³ and so you have to accept the consequences. Nearly every disorder has an anamnesis for which the individual to a certain extent bears responsibility. Whether certain rights should be restricted when an individual fails to exercise his or her own responsibility is itself a question requiring further discussion. Den Hartogh avoids getting too entangled in this discussion, by rightly pointing out that while the role of personal responsibility for one's own state of health is often very complex, in this case it only refers to the decision whether or not to donate.

Still another potential source of unease, however, relates to the assumption that the implementation of the system as den Hartogh presents it would at least not put anyone at a disadvantage. If the value of the bonus points is appropriately chosen so that it will only make a difference in case of equal medical suitability, the system is presented as a win-win situation. The registered donors end up higher on the waiting list when the donations are 'restricted', and non-donors - in the worst case - remain in precisely the same situation as before. This is problematic in two respects. For one, as indicated, it is precisely the guarantee of a better position that is regarded as a stimulating factor for registration as a donor. We mentioned above that this guarantee may be too weak. Two, it is questionable that it would not set anyone back. This is only the case if you assume that the organs intended for 'restricted donation' would otherwise be lost, i.e. that in the current system they would not be donated. Those who are registered donors in the current system, however, may be among the few motivated enough to register to restricted donation. Given their commitment to decision-making regarding donation, it is conceivable that they will reflect on complying with the reciprocity option and that they will be willing to take trouble to adjust their registration. Hence, the possibility remains that these individuals are largely the only people who would register as donors and who would include

the option of restricted donation in the new system. This way, the amount of available donors might not change. The number of organs that the so-called ‘parasites’ could then count on would greatly decline, and this would indeed mean a step backwards for them. Of course den Hartogh would see no problem in this, because it is the indirect consequence of their own decision not to donate. But is it really that simple? What about people who cannot or are not allowed to donate? As Arthur Caplan points out in the discussion regarding Life Sharers - it would mean a step backwards for the people who are already on the waiting list because, in view of their poor health, they are simply no longer capable of donating organs⁴⁴. What should be done, moreover, with minors who come to need a transplant but who have not yet registered (or who have not yet even been *able* to register) as donors?

Finally, the reference to the concept of Samaritan duty is not sufficiently compelling. The introduction of this concept is helpful in reminding us of our shared societal responsibility to avoid or minimize suffering wherever and whenever possible. However, the three criteria den Hartogh lists are too vague and not uniquely applicable to the duty of donating organs. Particularly the first criterion, that a person must be in ‘serious need’, is not unproblematic. How much loss of quality of life is enough for the criterion to be satisfied? This is not to deny that people on the waiting list are often very badly off, or to say that people who are not suffering enough according to the criterion should not get an organ transplant. But it is very difficult to draw the line between cases of serious need and others, especially given the fact that many waiting list patients can temporarily be helped by other, imperfect means (dialysis, medicine, etc.). What is of serious need to one individual may not be perceived by another in the same manner. Moreover - and with regard to the second criterion of this duty - even if it can be agreed that the help someone offers by donating his or her organs is of little cost, the analogy with the drowning case is relatively weak and inconsistent with other means of offering life-saving help within and beyond health care. As Hamer and Rivlin suggest in their discussion of John Harris’ controversial suggestion to *oblige* organ donation, for instance:

Although most of us would probably find someone who did not stoop to pull a drowning child from a shallow pond to be morally lacking, we do not give all the blood we can give (...), we do not give all our spare money to charity, we do not all place ourselves on the bone marrow register. And we do not think ourselves morally blameworthy if we spend some of our time idly watching television or going on holiday rather than working for the underprivileged.⁴⁵

More importantly, even less demanding examples of donating just 5 per cent of our income to charity, or of donating blood merely once a year are not regarded as Samaritan duties, while arguably just as much in accordance with the three criteria as donating organs after death.

2.4 Conclusion

Steering organ allocation towards those who are themselves willing to donate organs is both an ineffective and morally questionable means of attempting to improve procurement and allocation of transplantable organs. Suggestions to harshen the criteria of eligibility to a life-saving transplant will nonetheless persist as long as there is a shortage of organs. It is likely that, along with an efficient procurement procedure, a greater number of donations and transplantations will rest predominantly on diminishing the percentage of family objections. As we will see in the subsequent chapter, however, shortage is inevitable if we are to limit the pool of transplantable grafts to those obtained from human donations.

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3 Organs galore: an overview of emerging alternatives to the donation model

Abstract

While the impact of continuous efforts to increase the pool of postmortem donors should not be underestimated, it has been suggested that cadaveric donation will never be the final solution to the organ shortage. If we wish to augment the transplantation rate substantially, efforts should be made to maximize living donation or to find alternative sources of transplantable grafts. This chapter gives an overview of various approaches that are currently being explored: (a) the commercialization of grafts from living providers; (b) the development of artificial replacements; (c) the use of stem cell technology to ‘grow your own’ grafts or to support failing tissues or organs. The intention of this chapter is to demonstrate in which respect those alternatives are likely to fall short of providing a substantial pool of transplantable organs and tissues in the near future. The current lack of viable alternatives motivates a persistent interest in the development of suitable animal-derived cells, tissues and organs for transplantation.

3.1 Not enough deaths to save the dying

The impact of continuous efforts to increase the pool of postmortem donors should not be underestimated and it will remain pivotal that donation is further encouraged and the procurement process further optimized. That said, it is important to understand that, however much the procurement system is improved, cadaveric donation will never be the *final* solution to the organ shortage. The largest study of the organ donor potential ever conducted in the US indicates that the supply of cadaveric donor grafts unavoidably falls short, even in the theoretical case in which *all* brain-dead potential donors become actual donors and the demand for organs remains constant¹. Evans has expressed a similar prognosis^{2,3}. Indeed, it is very unlikely that the demand rate will remain constant. During the past years, the number of patients awaiting transplantation has grown exponentially. This trend is unlikely to disappear because the conditions for which transplantation is the appropriate treatment are constantly expanding. Furthermore, the prevalence of brain death is rare. Most clinically brain dead patients owe their state to a cerebrovascular accident or a severe cranial/brain injury. The number of potential postmortem donors is declining inversely proportional to the heightening of safety measures to prevent motor vehicle accidents. Also, the major reason for non-recovery from postmortem donors is poor organ quality. Nearly 50 per cent of the organs of brain-dead potential donors in the US are simply unsuitable⁴.

If we wish to augment the transplantation rate substantially, efforts should be made to maximize living donation or to find alternative sources of transplantable grafts. This chapter provides an overview of various approaches that are currently being explored for this end: (a) the commercialization of grafts from living providers, (b) the development of artificial replacements, and (c) the use of stem cell technology to ‘grow your own’ grafts or to support failing tissues/organs. Realizing that particularly the latter technologies may improve substantially over time, the intention of this chapter is to demonstrate in which respect those alternatives are likely to fall short of providing a substantial pool of transplantable organs and tissues in the near future. The current lack of viable alternatives motivates a persistent interest in the development of suitable animal-derived cells, tissues and organs for transplantation.

3.2 Maximizing living ‘donation’: commercialized transplantation

3.2.1 Transplant tourism

In 1983 Dr H. Barry Jacobs founded the International Kidney Exchange, Ltd., offering thousands of US transplant centres to serve as a kidney broker for end stage renal diseased patients⁵. The initiative never materialized but generated heated debate and was addressed in the National Organ Transplant Act of 1984:

It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce.⁶

By 1989, 20 other nations, the World Health Organization and a range of international transplant associations had passed similar prohibitions^{7,8}. Commercial dealings in human body parts have also been outlawed by the Council of Europe’s Convention on Human Rights and Biomedicine (article 21)⁹. A study of the legislation of 24 countries (Australia, Austria, Belgium, Britain, Canada, Denmark, Finland, France, Germany, Greece, Hong Kong, India, Ireland, Italy, Japan, Luxembourg, Netherlands, Portugal, Singapore, Slovakia, Spain, Sweden, Turkey, US) shows that all those nations have a general prohibition against direct commercial dealings in human organs¹⁰.

That rare manifestation of international legal consensus has not precluded a black market trade of organs. Ever since the 1980s there have been continuous indications of ‘transplant tourism’, with prosperous patients travelling to other parts of the world to purchase the transplantable kidneys for which they would otherwise have to wait indefinitely in their resident country. The first ‘tourists’ were mainly Asians and residents of Gulf States who travelled to India - a nation that severely criminalizes organ trade -, China and other parts of Asia (e.g. Malaysia, Singapore, Hong Kong, Korea)¹¹. Access to the potentially life-saving therapy has been rendered a matter of ‘seek and ye shall find’ over the entire world. In three years time, 300 Israeli were reported to have received kidneys from donors in Estonia, Bulgaria and Turkey at an average price of \$40,000¹². Allegedly, whole transplant teams travel from places where commercial transplants are prohibited to more permissive places to facilitate the surgery¹³. Kidney donors are often solicited through advertisements in the newspaper¹⁴. Alternatively, worldwide, Internet sites have been launched to provide a venue in which potential recipients can make electronic pleas for an organ and hope to

attract a donation (whether paid or not) from the general public^{15,16}. In 1999 a “fully functional kidney” was put up on the Internet auction site eBay, bringing in bids of up to \$7.5 million until the company interrupted the sale^{17,18}.

The conviction that financial inducements are necessary to motivate living donation has become increasingly prevalent. Economists argue that shortage is inevitable whenever the price of a good is held below its market demand. Nobel Prize-winning economist Gary Becker and Julio Elias estimate that by pricing kidneys at \$15,000 and liver segments at \$32,000 (due to the higher health risk for the donor), enough donors could be attracted to close the gap between supply and demand¹⁹. Aside from the potential impact that system is believed to have on the transplant rate, the argument has been put forward that regularization of a trade system should also be considered in order to protect patients from the current dangers of the clandestine free trade²⁰. However, those proposals run up against firm ethical, legal and cultural barriers.

3.2.2 Arguments against commercialization

To many, the notion of financial inducement for donation is subject to serious ethical perversions. Common criticisms refer to fears that a market-driven organ supply would undermine the spirit of altruism and render human beings and their parts mere commodities. It is also feared that such a practice would coerce the poor to jeopardize their health and benefit only the rich.

Ever since the use of the first cadaveric organs for transplantation, organ procurement has been presented as a ‘gift of life’, linking the connotations of organ ‘donor’ and ‘recipient’ to notions of generosity and altruism. To some, references to charity constitute the pillars of the social and ethical meaning of the whole transplantation business and form the prerequisite for public support²¹. It is also feared that abandoning the view of donation as a social duty will sabotage the development of cadaveric and related living donation. This would be particularly harmful for transplant programs involving those grafts that can only be obtained from cadaveric donors. Other appeals to preserve the ‘gift rhetoric’ indicate the psychological advantage of this approach. Sells, for instance, refers to the way in which altruistic voluntary donation contributes to positive self-esteem²². According to Joralemon, a non-materialist conception of the body and the act of generous sacrifice promotes a meaningful connection of the organs to the self²³. Others confirm the belief

that, at least symbolically, organs help define who we are, and hence, that the selling of an organ is the selling of parts of the self²⁴. It fundamentally renders the body “dis-organized”²⁵ and reduces its parts to alienable, economic products²⁶. It is also argued that paid donation would entice only poor people to provide the kidneys, whereas access to the organs gained would be restricted to the rich. Additionally, it is claimed that the consent of the donor cannot be voluntary, because it is motivated by poverty and despair. By offering a substantial financial ‘reward’, a potential organ provider is encouraged (or perhaps even forced by other stake holders) to do something he or she otherwise would not be inclined to do. Worse still, the retrieval of a kidney or liver/lung segment goes against the donor's best interests and makes him or her disproportionately susceptible for certain health risks.

3.2.3 Arguments in defence of commercialization

The grounds for condemning the commercialization of living donation have been countered with strong arguments in defence. For instance, the idea that selling body parts would threaten one's sense of self is rebutted in reference to the increasing and overtly commercial transactions of human sperm and oocytes²⁷, which relate much more strongly to personal identity than do internal organs (apart from the brain). Furthermore, it is not particularly the selling of organs that ‘de-organ-izes’ the self, it is the ability to remove and replace the organs. In other words, it is the practice of transplantation itself - rather than the commercialization of body parts - that is being rejected. In addition, the view that body parts are intrinsically unrelated to a monetary value is hardly consistent with the fact that there are now more than 50 artificial body parts for sale²⁸.

As the discussion of den Hartogh's proposal also demonstrated, the imperative to depend on public ‘goodwill’ is not directly compelling. Indeed, Siminoff and Chillag ask us to consider the adverse consequences of the ‘gift of life’ metaphor²⁹. In the footsteps of Fox and Swazey³⁰, they refer to Mauss' Gift Exchange Theory that clearly implies that gift-giving is related to expected reciprocity. In acknowledgment of the fact that the gift of life is not commensurable, transplant recipients often experience an overwhelming sense of debt³¹. A grave sense of responsibility for their second chance of life also occurs when the donor organs do not function appropriately in their new host environment, particularly when derived from a living donor. Another argument against the appeal of ‘altruism’ is that the metaphor of the ‘gift of life’ is in itself inconsistent with the fact that the ‘gift’ is

always related to charges for the transplant services and the medication³². Others have revealed the paradox that the donor is the only one involved in the field of transplantation who is not in one way or another rewarded for his or her services³³. In the knowledge that donors suffer financial stress from donor-associated costs and difficulties in re-entering employment^{34,35}, it can be argued that it is exploitative not to reimburse the donor at all. Furthermore, the metaphor is ineffective: family consent to postmortal donation is rarely motivated by the willingness to make a gift, but rather by the hope that the deceased will somehow live on³⁶.

On the other hand, a trade in organs does not directly oppose the gift-giving model of organ donation. Robert Veatch makes that case referring to the fact that, as early as 1968, it was argued appropriate for society to take viable body parts from the dead without formal permission³⁷. In contrast to that approach, a market model is more consistent with the contemporary emphasis on the rights of the individual to consent or to refuse. Both consented donation and trade models are based on the principle that our body belongs to us, and that we enjoy the right to decide whether or not to 'give' our organs away. Viewing parts of the body as matters of property, which the individual may dispose of, at once also limits the extent to which others can exploit it. As Andrews argues, by treating body parts as the individual's property, there is a legal basis for protections that may not exist under themes of privacy, autonomy, assault, or infliction of emotional distress. This ownership will become increasingly important in light of requests to preserve bodily materials for future medical use, such as bone marrow for gene therapy³⁸.

The idea that organ trade involves severe abuse of the poor partly stems from urban legends. For years, sensational stories have been circulating of street children in Honduras, Guatemala, Argentina and Brazil being kidnapped and murdered for their organs. These allegations remain without evidence and are likely to reflect the mistrust of certain populations against the western transplantation enterprise. This mistrust has a historical root. At the turn of the 18th century, corpses obtained by grave robbers ('body snatchers') were sold to anatomists in lucrative black markets during times of shortage³⁹. Alternatively, as suggested by the Bellagio Task Force, the urban legends are inspired by past incidences of child abduction for sexual abuse or for illegal adoption⁴⁰. In Guatemala, particularly, inhabitants are convinced that foreigners steal children and this belief has merged with stories of Americans taking babies for their organs⁴¹.

That is not to say that there is no exploitation of organ providers in current trade systems. Most black markets in developing nations involve brokers whose very intent it is to exploit the poor. Nonetheless, it is not an essential part of a market system: “It is one thing for people to have the right to treat their own bodies as property, quite another to allow others to treat a person as property.”⁴² Indeed, proponents of a regulated market system believe that regulation is the only way to eliminate currently concealed forms of exploitation. Suitable oversight could guarantee fair reimbursement for and fully informed consent from the donor. Moreover, whereas the organs would be retrieved by a market approach, implementation of a welfare system for the distribution of the obtained supply could guarantee equitable access for the poor.

A famous argument in favour of organ trade is that prohibition perpetuates rather than prevents the exploitable position of the potential vendors. Defenders of this view regard kidney trade as an opportunity for the poor to enhance their position from an *in se* exploitable situation. Even underpaid vendors may use the extra income to change future economic prospects or to broaden their opportunities. In a London court trial of doctors involved in organ trade, one of the kidney vendors was a Turkish man who needed the money to buy medicines for his daughter who was suffering from tuberculosis. Poor and unemployed, he maintained that this was his only opportunity for saving her⁴³. This generates the idea that the problem is not the selling of organs, but rather the reasons for wanting to sell organs. Radcliffe-Richards *et al.* make that point as follows:

(...) trying to end exploitation by prohibition is rather like ending slum dwelling by bulldozing slums; it ends the evil in that form, but only by making it worse for the victims. If we want to protect the exploited, we can do it only by removing the poverty that makes them vulnerable, or, failing that, by controlling the trade. There is much more scope for exploitation and abuse when a supply of desperately wanted goods is made illegal.⁴⁴

Critics may emphasize that the financial incentives inhibit full acknowledgement of the health risks associated to living organ donation. There is indeed a small, but real risk for the living donor, particularly for donations of liver segments. According to a systematic review of the literature on adult-to-adult living donor liver transplantation up to January 2004, donor mortality was 12 to 13 in about 6,000 procedures (0.2 per cent), with a higher risk (0.23 to 0.5 per cent) for right lobe donors⁴⁵. Given the short history of living donor liver transplantation procedures, little data are available regarding long-term outcomes.

Against that, it must be noted that the highest morbidity rates for donors have been reported in clandestine trades in developing nations, precisely due to the lack of a control mechanism, which would guarantee proper medical care. Lack of or deficiency in HLA-matching and pre-transplant workup of recipients and donors often leads to poor outcomes, including serious infectious complications such as viral hepatitis^{46,47} and HIV⁴⁸. Non-infectious medical complications, including congestive cardiac failure, post-transplant diabetes mellitus and acute myocardial infarction, have been reported among patients returning to Israel after receiving living unrelated donor transplants in Iraq or India⁴⁹. In a survey of vendors in Chennai, India, 86 per cent of the respondents reported deterioration in health after kidney retrieval⁵⁰.

Furthermore, it has been remarked that the risks are overemphasized once the notion of financial compensation is considered⁵¹. The normal risk of donating a kidney at the age of 35 is comparable to the risk associated with driving a car to work 16 miles a day⁵². Moreover, if we are to object that people opt for this health risk, our objection should be consistent with other hazardous behaviours that poor people are disproportionately compelled to conduct: for instance, their decisions to buy a cheaper but less safe car, or to take a physically dangerous job such as high-steel construction⁵³. A strong case can thus be made that “loss of autonomy results from poverty, not from paid donation.”⁵⁴

3.2.4 Reality check: an illustration from Iran

The arguments in defence of commercialising organ donation are sufficiently compelling to warrant further discussion. Suffice it here to conclude that the prohibitive forces nevertheless remain strong, rendering it unlikely that a trade regulation will be endorsed in Western nations any time soon. As mentioned in the first chapter, initiatives to ease the prohibition have been restricted to proposals that allow limited reimbursement of the donor's time, expenses and recovery.

Aside of China, which, we noted, plans to ban the trade of organs from executed prisoners, there is one nation in which organ trade is supported on a governmental level. In Iran, where the cadaveric transplantation act is rejected, living unrelated renal donor transplantation amounts to approximately 90 per cent of all transplants⁵⁵. The great majority of ‘donors’ are vendors. The procedure set off as ‘rewarded giving’ to donors by recipients directly. In 1997 a law was passed, instructing the payment of 10 million Rials

(the equivalent of \$1,219) to each vendor. The money is obtained from the governmental budget, allowing equal access for all citizens to the purchase of a kidney transplant. In addition to this sum of money, the prospective recipient often offers the vendor extra advantages, such as employment opportunities. As a result of these enticements, the waiting lists for candidate recipients have dissolved⁵⁶ and have ironically been replaced by long donor waiting lists⁵⁷.

Nonetheless, this example appears to be bad advertisement for market proposals in terms of donor welfare and the overall impact on transplant programs. Despite governmental oversight of the trade and the fact that the compensation is substantial with regard to the local life standard, the effects of the transplants are often adverse for the donor. Zargooshi reports that almost none of the criteria for acceptable living unrelated renal donation and follow-up are met⁵⁸. Moreover, in his survey of the motivations of Iranian kidney vendors (n=100), the majority of the donors claimed that they had not been able to use the money to free themselves from poverty or debt. In a different survey on the quality of life of vendor donors (n=300), Zargooshi found that persistent poverty prevented the majority of the donors from attending follow-up visits⁵⁹. Vending also had negative effects on employment in 65 per cent and caused severe postoperative depression for 71 per cent of the vendors. Almost half of the vendors surveyed would opt for a shortening of life by more than ten years and substantial loss of property in return for their preoperative condition⁶⁰. The respondents referred to three vendors who set themselves on fire after becoming severely depressed because their life conditions remained unaltered. This particular example also partly confirms the prediction⁶¹ that living unrelated donor programs will hinder the growth of cadaveric transplant programs and living related donation. All *related* donors demanded money for their kidney from their family member and felt that their offer deserved priority over that from strangers.

Remaining controversy surrounding organ trades - and the potential adverse effects on acquisition of other grafts that cannot be obtained from living donors - have propelled efforts to fabricate organs and tissues from scratch or to provide engineered mechanisms of support for the damaged body parts.

3.3 Artificial organs and support devices

For decades now, research has focused on developing implantable artificial organs to augment or replace organ functions. While that has resulted in several devices offering temporary support of failing organs, the current stage of technology is still lacking in the ability to provide optimal and permanent solutions that sufficiently enhance quality of life.

3.3.1 Artificial kidney and dialysis

A first important step towards the creation of artificial replacements was the development of the artificial kidney by Kolff in 1944. The machine was created to substitute the malfunctioning kidney's main filtering function. The procedure involved separating particles in the patient's blood by differences in ability to pass through a semi-permeable membrane. The successful diffusion of toxins and waste products had a profound impact on pushing back the mortality rate related to kidney disease⁶². With the first kidney transplantation trials, the machine provided both pre- and postoperative support of the recipients.

Kidney dialysis remains an effective means to stretch time until a transplantable kidney becomes available. The treatment nevertheless has severe effects on the patients' quality of life. Patients are connected to the external machine for a minimum of 12 hours a week. Aside of their being hospital-bound, they must follow strict diets and limit their intake of fluids. The dialysis machine does not automatically adapt to changes in a patient's body functions. Hence, the blood must be constantly monitored and laboratory tested. While the kidney is more than just a filter, the dialysis does not compensate for those other lost functions. As a result, many early dialysis patients developed severe complications, including bone disease, anaemia and even mental deterioration ('dialysis dementia')⁶³. Those effects were caused by respectively the loss of vitamin D conversion (which regulates the absorption of calcium), deprivation of erythropoietin (EPO) production (a hormone which stimulates bone marrow to make oxygen-carrying red blood cells) and toxicity due to the presence of aluminium in the dialysis fluids. Given the fact that many of the organ's complex functions depend on integration with other organs, the development of fully implantable kidney duplicates seems remote. The closest treatment currently available is peritoneal dialysis, which uses a patient's own membrane around the intestines to diffuse and withdraw the body's fluids through implanted catheters. The

technique enhances mobility, but it requires an enormous effort of the patient to routinely adopt sterile technique.

3.3.2 Liver support systems

Although complete understanding of its many functions is still lacking, the liver is known to play a major role in metabolism, drug detoxification, glycogen storage, plasma protein synthesis and bile production. Accumulative toxicity caused by liver failure leads to a wide range of complications, ultimately resulting in coma and death. However, because of the liver's regenerative abilities, liver failure is often reversible if a temporary liver substitute is provided⁶⁴. Two main approaches have been used to reinforce liver regeneration: non-biological and hybrid biological artificial support⁶⁵.

Early artificial means to increase the survival rates of patients with liver failure relied on an external bank of activated charcoal columns to filter out harmful substances from the blood. However, that technique showed no improvement in long-term survival since it did not replace other liver functions. Alternatively, plasma exchange - a technique in which a patient's plasma is separated from the blood and replaced with an equivalent dose of fresh frozen plasma - allows for both removal of hepatic toxins and replacement of various beneficial factors. Here too, no significant improvement of patient survival has been observed⁶⁶. Conversely, reports of substantially prolonged patient survival have been indicated in randomized, controlled trials of the Molecular Adsorbents Recirculating System (MARS)⁶⁷. That system consists of an albumin-enriched dialysate, charcoal filter and ion exchange compound that filter out albumin-bound toxic metabolites. However, MARS only substitutes for the filtration and detoxifying function of the liver and may even remove essential factors that are involved in hepatic regeneration⁶⁸.

Both extracorporeal whole liver perfusion and hybrid biological artificial support have been applied to replace the liver's synthetic functions, metabolic role, and removal and detoxification of harmful substances. The main merit of this technology is that it may bridge time to allow for full rehabilitation of the liver's normal functions or to find a donor liver for transplantation. Extracorporeal perfusion involves the use of an external liver through which the patient's waste products are metabolized. Due to shortage of human livers, mainly pig livers are being considered in this area. Given that this is a form of xenotransplantation, this procedure will be discussed in the subsequent chapter. In hybrid

biological artificial support, isolated, metabolically active liver cells - either implanted in the patient or perfused extracorporeally within a synthetic framework - replace liver functions⁶⁹. The best results have been obtained with devices in which the hepatocytes - through which the patient's blood or plasma is passed - have formed an aggregation of functional liver tissue. Such extracorporeal bioartificial support containing active human cells has also been developed for pancreas and kidney^{70,71}. Due to the scarcity of human cell supply, however, recent interest in bioartificial devices has focused on the use of porcine cells or human stem cells.

3.3.3 Lung replacement technology

The earliest efforts to develop implantable artificial lungs were reported in the 1970s⁷². Nevertheless, to this day, chronic irreversible pulmonary failure is only treatable by lung transplantation. Unlike liver and kidney substitutes, artificial lung support is inadequate to serve as a bridge to transplantation⁷³. The difficulty lies in the need to provide persistent oxygen supplies rapidly enough while adapting to changes in demands on oxygen requirements and carbon dioxide removal.

For decades, mechanical ventilators have been used to deliver volumes of air to the patient's lungs through a tube in the windpipe. The level of oxygen must be adapted continuously to meet the patient's needs. The technique is aggressive and can cause a build-up of free radicals or overstretch scarred lung tissue⁷⁴. An advanced procedure, the extracorporeal membrane oxygenator (ECMO), passes oxygen-poor blood from large veins through an oxygenator and returns the oxygenated blood to the heart or directly to the lungs. While this device has been used successfully on patients affected by severe respiratory failure, it is non-ambulatory and has all the other discomforts related to extracorporeal assistance. Moreover, the procedure is complex, expensive, time-consuming and labour-intensive and offers many sites for bacterial infection⁷⁵. Intravenous systems - such as the intravascular oxygenator system (IVOX) and the intravenous membrane oxygenator (IMO) - have also been developed. They can be inserted into the patient's largest chest veins and allow for oxygen-carbon dioxide transfer of the blood within the implanted system. However, those systems imply limited space for gas exchange and cannot function independently as a bridge-to-recovery or transplant. Improved, larger versions of the model replace a patient's non-functional lung and can be fully contained

within the chest cavity. Preliminary experiments suggest sufficient gas exchange supply, but it is unknown how long the device can endure implantation⁷⁶.

3.3.4 Total and partial heart replacements

The heart can be considered the least complex of the solid organs: a muscular pump supplies the circulatory system with oxygenated blood from the lungs and transports nutrients, wastes and gases to and from all cells in the body. Total heart replacement, however, remains a challenge, despite significant advances in the technology over the past 10 years. Although the first successful bridge to cardiac transplant was through the use of a total artificial heart (in 1969)⁷⁷, best results are currently obtained by a range of devices which offer partial heart support.

Left ventricular assist devices (LVAD) assist in the pumping of the left ventricle of the heart in patients with left ventricular failure. With the original heart still in place, the regulation of the rhythmic pumping pattern and responses to signals from the rest of the body are maintained. LVADs have been successful both as bridges to cardiac transplantation and as long-term support⁷⁸. The first of such devices - the Heartmate implantable pneumatic (IP) LVAD - was accepted for routine use in 1994⁷⁹. In ten years time, an estimated 7,000 LVADs have been implanted worldwide⁸⁰. Modern models are totally implantable and provide quiet continuous flow. Nevertheless, the success is not unquestioned, with concern remaining over their inability to manage the patients' liability to irregular heartbeats⁸¹. In addition, infections, inflow valve insufficiency, bleeding, renal and multi-organ failure are included among the possible complications⁸². Furthermore, this procedure is not suitable for therapeutic use in patients with severe biventricular failure.

The first recipients of a *total* artificial heart (TAH) succumbed to infectious complications. With the development of more sophisticated forms of immunosuppression, long-term therapy appeared feasible. In 1982, the Jarvik-7 - a total, biventricular artificial heart - was implanted into a 61-year-old patient suffering end stage congestive heart failure⁸³. The implant was made from aluminium and polyurethane and consisted of two separate ventricles, which were grafted to the native cavities and great vessels. The power supply depended on an externalized, 400-pound air compressor. Post-transplant, the patient struggled with many life-threatening complications and finally surrendered to multi-organ failure after 112 days⁸⁴. The US Food and Drug Administration suspended the use of this

model in 1990. Advanced models entered the clinic from 1993 on, and have shown survival rates sufficient to bridge time for a transplant in 70 to 90 per cent⁸⁵. Still, mortality and morbidity were most commonly related to multi-organ failure, renal dysfunction and infection. The only TAH replacement designed for *permanent* therapy to date is AbioCor⁸⁶. Clinical trials of this first fully contained artificial heart initiated on 2 July 2001. With total implantability, the sites for microbial infection are minimized and comfort is maximized⁸⁷. As the device depends on an external battery pack, methods are also being designed to circumvent this^{88,89}. However, the size of the device (comparable to a grapefruit) does not facilitate implantation in smaller patients⁹⁰. Furthermore, its rhythmic movement burdens the surrounding, particularly softer connective tissues. The trial results of the use of AbioCor TAH have not been very encouraging. In 2003 only two of the eleven recipients of such a heart were reported to be alive. The others died within an average of five months. One recipient's widow sued the company claiming that her husband "had no quality of life and his essential human dignity had been taken from him."⁹¹ No cardiac replacement device that stands the test as a destination therapy has been developed yet. A TAH that can regulate the flow rate according to internal signals such as those from the central nervous system, is not achievable by the current state of science⁹². That renders the need for a donor heart transplant inevitable.

3.4 Bioengineered regeneration of tissues and organs

3.4.1 Regenerative medicine: a look into the future

Regenerative medicine is the most promising future therapy in terms of restoring or replacing lost or damaged organs and tissues. It holds the prospect of constructing transplantable grafts that fulfil the physiologic and metabolic requirements better than mechanical and even donated human substitutes^{93,94}. The technology consists of the combined use of living cells with regenerative capacities and tissue engineering techniques. Isolated living cells with regenerative capacities may be cultured outside the body and implanted *in situ* in the patient as a prospective therapy for a variety of diseases, such as Parkinson's and Alzheimer's disease, diabetes, rheumatoid arthritis and myocardial infarction⁹⁵. Future applications of regenerative cells would imply stimulating them to mimic the complex functions, mechanics and three-dimensional structures of whole organs. The ultimate advantage lies in the possibility to grow replacements that are

genetically identical to the prospective recipient and would thereby alleviate the need for immunosuppression.

3.4.2 Regenerative cells

Various sources of cells can be used for tissue repair and regeneration. They include embryonic stem cells, adult stem cells and mature (non-stem) cells, all of which may be autologous (same individual), allogeneic (same species, different individual), or xenogeneic (different species). The success of their regenerative abilities is dependent on the cells' potential to divide and produce more cells (proliferation) and to develop into various other cell types (differentiation). Due to the continuous cell specialization during embryonic development, the cells' levels of potencies can be distinguished in terms of the developmental stage in which they were produced.

Mature (non-stem) cells are found in humans after birth. They have the lowest proliferative potential and at the same time the highest level of specialization, thereby drastically restricting the number of cells that can be cultured and the range of tissues the cell cultures can support. Although the use of chondrocytes has proved successful in repairing cartilage and keratinocytes for treatment of burns⁹⁶, stem cells are a much preferred source for regeneration of multiple cell lineage tissues.

Adult stem (AS) cells, also found in humans after birth, can differentiate into a limited number of specialized cell types, typically the cell type of a particular organ/tissue or of the area in the body from which they emerged. These 'multipotent' cells can be found in specific places all over the body, including bone marrow, blood vessels, dental pulp, the digestive epithelium, the retina, liver, foetal chord, umbilical chord and even in the brain⁹⁷. Their natural role is to replace damaged or lost tissue, as illustrated by the daily renewal of 200 billion red blood cells by haematopoietic stem cells. Recent research suggests that AS cells have a greater plasticity and differentiation potential than previously expected. For instance, the differentiation of mesenchymal stem cells into mature hepatocytes and neural cells has been reported⁹⁸. Indications of increased AS cell plasticity have given rise to new procedures, including treatment of myocardial infarction by microinjection of haematopoietic cells and mesenchymal cells from the patient's own bone marrow⁹⁹. Progenitor cells (which are the most specialized stem cells) from bone marrow have been applied to treat cartilage and liver damage, spinal cord injury, and most

recently diabetes¹⁰⁰. Nonetheless, controversy remains whether the multilineages obtained are generated solely by the differentiation of a single stem cell or not¹⁰¹. Moreover, although many different kinds of multipotent stem cells have been identified, AS cells that could give rise to all cell and tissue types have not yet been found. There is also emerging evidence that those stem cells inevitably lose their ability to divide and differentiate at a certain point. Furthermore, AS cells are difficult to isolate, slow to culture *in vitro* and susceptible to DNA abnormalities.

Embryonic stems (ES) cells have the greatest differentiation potential and develop in early embryonic stages. Totipotent stem cells can be obtained from up to eight cell divisions and are the ‘mother cells’ of all embryonic cell types and extra-embryonic membranes. Pluripotent stem cells, which can be obtained from the inner cell mass of blastocysts (consisting of 50 to 150 cells), are more differentiated but maintain the capacity to generate virtually all cell types that make up an adult body. The trump of these cells is that they can be expanded almost indefinitely in an undifferentiated state *in vitro* and manipulated to generate embryoid bodies, which are cell aggregations that contain all three embryonic germ layers (endoderm, ectoderm, mesoderm)^{102,103}. The isolation of human ES cells¹⁰⁴ and the successful differentiation into neurons, skin, cardiomyocytes, pancreatic, haematopoietic, endothelial and muscle cells^{105,106} suggest the viability of manipulating those cells to produce an unlimited supply of practically all tissue and organ types.

Although regenerative medicine is considered the holy grail of medicine¹⁰⁷, the major difficulty restricting its clinical use is the need to learn how to instruct a stem cell to differentiate into only the cell type required¹⁰⁸. Unanswered questions regarding the manipulability of ES cell growth and differentiation retain the research largely to an experimental stage. Additionally, it is not known how the stem cells should be implanted so that they would take up the optimal anatomical position. Moreover, both AS cells and ES cells pose an as yet uncontrollable risk of forming unwanted tissues and tumours. In comparison with AS cells, however, ES cells have some significant drawbacks. They are obtained from a non-autologous source and may thus engender a severe immune response¹⁰⁹. Furthermore, human ES cell lines are necessarily derived from either leftover embryos generated through *in vitro* fertilization or from embryos created especially for the purpose of stem cell research¹¹⁰. The destruction of blastocyst-stage embryos for the harvesting of ES cells has raised tense ethical and political concerns.

3.4.3 Therapeutic cloning

The immunological barrier to the use of human ES cells is theoretically removable through therapeutic cloning, through parthenogenesis, or through the creation of immunotolerant ES cell lines¹¹¹. Particularly therapeutic cloning - also called somatic cell nuclear transfer - is considered to be a feasible approach to create an inexhaustible supply of host-compatible replacement tissue¹¹². The procedure consists in transferring the nucleus from a mature donor cell into an enucleated oocyte. The oocyte cytoplasm has the capacity to 'reprogram' the DNA of the nucleus so that the process of cell division is recommenced and stem cells are generated. The technique holds the prospect of deriving ES cells from the blastocysts and producing healthy, functional substitutes of the donor cell that can then be re-transplanted into the specific damaged sites of the patient's body. As the cells are obtained from the donor's cell nucleus, they are genetically identical to all cells of that individual's body and will not undergo rejection after transplantation. The procedure, as a way to provide cells and tissues for transplantation, is also subject to less *cultural* rejection (objections on the basis of ethical and/or social considerations) in comparison with reproductive cloning¹¹³. Contrary to reproductive cloning, the blastocyst is not transplanted back to the uterus. The first demonstration of the use of therapeutic cloning for the regeneration of tissues *in vivo* was the successful production of cloned, host-compatible bovine renal and cardiac muscle structures¹¹⁴. In May 2005 Woo Suk Hwang and colleagues documented the successful cloning of 31 human embryos and the production of 11 human ES cell lines¹¹⁵. That report had us believe that we were well on our way to acquiring various self-compatible cell types that could be employed in a wide range of replacement therapies. Unfortunately, Hwang's cell lines were fabricated¹¹⁶ and the first human ES cells obtained from cloned embryos still lies ahead. Although research in this field persists, important improvements are required in the many steps involved in nuclear transfer before we can readily produce viable sources of cells.

3.4.4 Organogenesis

Once an adequate amount of stem cells can be expanded from a cloned, compatible source, the challenge will be to reproduce the complex micro-anatomical structures and functions of multi-tissue organ structures¹¹⁷. They cannot be generated through the potencies of cell grafts alone. The outlook of growing solid organs (organogenesis) from tissue specific organoids (an organisation of cells into an organ-like structure) is aided by

recent advances in bioengineering techniques¹¹⁸. It is hoped that further progress will allow to seed sufficient amounts of suitable cells onto biodegradable scaffolds and to coax them to proliferate and specialize into an organized array of the desired living tissue type.

Over thirty different tissues have been developed over the past two decades, many of which have been shown to function in animal models^{119,120}. Various types of skin¹²¹, cartilage replacement¹²², bone¹²³ and blood vessels¹²⁴ have been successfully developed for clinical use in humans. Recent advances have also been made in the tissue engineering of more complex, composite tissues through the conjunction of two or more cell lineages¹²⁵. The engineering of gastrointestinal and urologic tissues is in an early stage¹²⁶. Full-sized, three-dimensional, functional organs have not been generated yet.

The greatest difficulty is creating the various tissue components that form a particular organ and coaxing them to function as a harmonious whole. While heart valves have been constructed, the outlook of constructing coronary vessels, muscle and other miscellaneous parts in a multi-chambered bioreactor, by contrast, remains remote¹²⁷. Biomaterials provide a functional three-dimensional framework on which the cells can be seeded and grown. Theoretically, these structures would, once implanted, allow the cells to synthesize into new tissues while providing an intermediary for the transport of cells and appropriate bioactive factors to desired sites in the body¹²⁸. However, the development of proper scaffoldings encounters very high requirements. In early stages, the biomaterial should support the matrix structural integrity of the engineered tissue. In later stages, however, the scaffold should biodegrade at a rate that coincides as much as possible with the rate of new tissue formation¹²⁹.

Furthermore, to sustain the growth and development of organogenesis *in vivo*, the engineered tissues must integrate and function with the patient's circulatory and nervous system. In theory, a capillary network can be pre-constructed in the tissue *in vitro* and afterwards be connected to the patient's circulatory system by microsurgery. This concept was pioneered by Vacanti and colleagues and has resulted in the gradual production of capillary patterns with a biodegradable elastomer^{130,131}. 'Printing technology' has emerged as a fascinating alternative in the long run. It consists in using an inkjet mechanism to print precise volumes of single cells and spherical cell aggregates - 'bio-ink' - into successive layers of biodegradable gel. Theoretically, this technology could allow the printing of a branching vascular tree as part of the aggregate organ-forming structures.

The research has advanced to the stage in which endothelial cells (the cells that line blood vessels) are printed in a set of stacked rings¹³².

3.4.5 Nonhuman animal growth environments

Cascalho and Platt have argued against the feasibility of growing vascularized and innervated organs inside the patient due to the burden the tissue growth would impose on the already affected system^{133,134}. They suggest the use of animals as growth environments for the completion of organogenesis. The procedure could consist in transplanting early-staged human embryonic organs (organ primordia) into an animal and allowing them to mature into compatible grafts for transplantation. Preliminary animal experiments suggest that animal organ primordia, obtained at the proper moment in embryonic development, automatically grow and differentiate along defined organ-committed lines¹³⁵. Hammerman has shown that renal primordia transplanted into animals also become vascularized by host blood vessels, excrete waste, and support life in animals that lack both kidneys^{136,137}.

The proposed approach presents one of the newest (and least developed) research plans of xenotransplantation science and is indicative of the persistent interest in this field. It suggests that the use of nonhuman animals either as hosts for human organogenesis, or as sources of genetically manipulated tissues and organs, stands closer to providing unlimited, fully functional replacements than any of the alternative approaches discussed above. Nevertheless, xenotransplantation has also been unexpectedly slow in moving to the clinic and that is due to both technical/biological and cultural constraints. The following chapter will outline the current constraints against conducting clinical xenotransplantation.

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PART TWO

XENOTRANSPLANTATION: PROBLEMS OF UNCERTAINTY

4 Barriers to clinical xenotransplantation

Adapted from: Ravelingien A. Xenotransplantation: an update on the safety of using pigs for transplantation. Flemish Veterinary Journal - Forthcoming.

Abstract

While xenotransplantation is generally regarded as an extraordinary field of contemporary medical research, there have been attempts to use animal cells and tissues for transplantation and transfusion in humans since the 17th century. Some of the first organs transplanted in humans were also derived from animals. A brief overview of the history of xenotransplantation reveals that, during the past, the greatest barrier to clinical success was hyperacute rejection: a complement-mediated response to the source animal tissue that results in the destruction of xenografts within minutes. In the past decade, great progress has been made in countering this form of rejection, but further success is thwarted by the gradual awareness of subsequent processes of rejection and physiological incompatibilities. Nonetheless, during this time, reluctance to move forward to the clinic has predominantly been related to the fear that xenotransplantation will unleash new infectious disease in the prospective recipient and his or her surroundings. This chapter gives an outline of the state of xenotransplantation science and the main barriers to its use as a successful clinical therapy.

To do nothing, or to prevent others from doing anything, is itself a type of experiment, for the prevention of experimentation is tantamount to the assumption of responsibility for an experiment different from the one proposed.¹

4.1 Standing the test of time

To assign a date to the outset of xenotransplantation, many will refer to the Greek legend of Daedalus, who grafted bird feathers to his arms and the arms of his son, Icarus, to escape from the island prison of King Minos. Perhaps surprisingly, the real history of xenotransplantation is also longstanding and features investigations that are themselves remarkable enough to have become legendary. In those experiments, all types of animals - frogs, cats, dogs, rats, rabbits, chickens, cockerels, pigeons, sheep, apes and pigs - have been considered as potential sources for clinical treatment².

The oldest xenotransplantations performed in humans involved transfusions of animal blood and were reported as early as 1628³. A famous example is the transfusion of a lamb's blood, conducted by Jean-Baptiste Davis, physician of King Louis XIV, and Paul Emmerez in 1667⁴. The recipient was a young man who suffered severe fever. The physicians were convinced that the symptoms had vanished as a result of the transfusion and subsequently applied the procedure for various other conditions, including mental illness. Indeed, as people believed that the lamb's blood would transfer the animal's docile and calm character, such xenotransfusions were a particularly popular treatment for problems of temper in 19th-century Britain⁵.

The first documentation on tissue xenotransplantation also dates from the 17th century, with the report of successful engraftment of a piece of canine cranial bone to repair a soldier's injured skull in 1668⁶. During the ensuing development of skin xenotransplantation, peculiar experiments included the grafting of a rat onto a crow's chest in 1860 and the grafting of skin flaps still attached to a living lamb to the back of a young burn victim in 1880⁷. A decade later, much of the interest in xenotransplantation concentrated on testicle grafts due to their alleged potential for human revitalization. Brown-Séquard, a 72-year-old French-American physician and physiologist, explored the concept in 1889, injecting himself with an extract of crushed testicles from dog and guinea

pig⁸. He claimed that the injections rejuvenated the strength and capacities that had been lessened through old age. Thirty-one years later, Serge Voronoff further developed those early attempts at endocrinology with the transplantation of slices of chimpanzee and baboon testicles in men⁹. Those transplants can be considered the “Viagra of the 1920s”¹⁰. The same surgeon also transplanted ape ovaries into women in an attempt to reverse menopause. In an extraordinary experiment, Voronoff even conducted the reverse transplantation of a woman’s ovary into a female chimpanzee and subsequently, although without result, inseminated human sperm.

Remarkably, the earliest attempts at clinical kidney and heart transplantation were also from animals to humans. Whereas the first human kidney transplant was performed in 1933, kidney xenotransplants were attempted at the beginning of the 20th century. In 1905 Princetau inserted slices of rabbit kidney in the kidney of a child with renal insufficiency¹¹. Having perfected the technique of vascular anastomosis (the surgical connection of the graft’s vessels to the vascular network of the recipient) that was developed by Alexis Carrel in 1902, Mathieu Jaboulay conducted what is considered the first true organ transplantation in 1906¹². The procedure involved connecting the renal vessels of a sheep and a goat kidney, respectively, to the bend of the elbow of two patients who were dying of renal failure¹³. Attempts to connect xenogeneic kidneys to the thighs or arms of human recipients persisted until 1923¹⁴. The first heart fully transplanted into a human was derived from a chimpanzee (named Bino) and carried out on 23 January 1964¹⁵. The transplant surgeon, James Hardy, was almost four years ahead of the first human-to-human heart transplantation, which was conducted by Christiaan Barnard in December 1967¹⁶.

The initial solid organ xenotransplantations were desperate measures to save terminally ill patients in cases where no alternative treatment was available. The survival rates of the first animal organ recipients were extremely poor: the patients died in a matter of hours or days after the surgery. With evidence of better results with allografts, allotransplantation rapidly became the approach to which most interest and research was dedicated¹⁷. Nevertheless, the appeal of using animals as sources of grafts resurfaced out of sheer necessity since human donors were similarly hard to come by before the implementation and endorsement of clinical brain death¹⁸. Between 1963 and 1984, a total of 39 kidney, liver and heart xenotransplants into humans were reported. The organs were primarily obtained from baboons, rhesus monkeys and chimpanzees, which clearly provided better results than organs from any other animal species¹⁹. In the early 1960s, use of

chemical immunosuppressants to counter rejection of human transplant grafts was initiated. Keith Reetsma was the first to apply specified immunosuppressive therapies in a nonhuman primate-to-human transplantation in 1963. One year later, the same surgeon obtained a 9-month survival in a recipient of a chimpanzee kidney showing no indication of organ rejection²⁰. This remains the longest survival ever recorded for the xenotransplantation of an organ. All other organ xenotransplants in humans reported to date have lasted no longer than 70 days²¹.

Probably the most controversial xenotransplantation ever performed was the transplantation of a baboon heart to a 12-day old female baby known as 'Baby Fae'. Leonard Bailey conducted the transplant on 26 October 1984 in the hope of rescuing the child, who suffered from hypoplastic left-heart syndrome, from imminent death. What at first appeared a successful and ambitious endeavour ended in the baby's death 20 days after the surgery due to rejection of the ABO-mismatched organ²². Thomas Starzl had also unsuccessfully attempted paediatric organ xenotransplants earlier, between 1969 and 1974. One of the trials included the transplantation of a chimpanzee liver to a 7-month-old boy. He only survived for 26 hours²³. The public outrage provoked by the death of Baby Fae suggests that Bailey's failed attempt was the last straw that broke the camel's back and marked the beginning of another *de facto* moratorium. The event caused heated public debate about the acceptability of using nonhuman primates as organ sources. It was also questioned whether the transplant had not intended clinical research rather than clinical treatment²⁴. Only in the early 1990's, again propelled by the scarcity of human donors, were organ xenotransplants given another go. By this time, progress had been made in the development of new immunosuppressive regimens and in genetic engineering techniques to manipulate donor-recipient incompatibility. During that period, five solid organ xenotransplants were performed, involving both baboon hearts and pig livers²⁵. One recipient of a baboon liver survived for 70 days. The other recipients died within a matter of hours or days. For all solid organ xenotransplantations, the immunological barrier was the principal hurdle to improvements in recipient survival rates.

More recent and successful clinical applications of xenotransplantation have consisted of cellular xenotransplants and *ex vivo* perfusions of diseased livers and kidneys. As explained in the previous section, with perfusion, the major blood vessels of the organs are connected and cross-circulated to an animal kidney or liver placed outside the body. The first cross-circulation experiment dates from 1967, and involved connecting the arm of a deeply hepatic comatose woman to the leg of a baboon. The baboon's kidney excreted

about 5 litres of the patient's fluid and allowed the patient to awake from coma²⁶. The potential to reverse deep coma related to fulminant hepatic failure has since been demonstrated with livers from various animal species²⁷. Attempts to restore or temporarily support the function of organs through linkage with animal organs, have also included extracorporeal perfusion of the heart and spleen and even oxygenation of the lungs²⁸. Alternatively, bioartificial liver devices, in which the patient's plasma is guided through primary porcine hepatocytes, have been applied to patients with acute liver failure^{29,30,31,32}. Some studies indicated improvement in survival; sufficient enough to bridge time for a liver transplantation or for the patient's own liver to recover^{33,34}. However, a general review of the clinical experience in extracorporeal pig liver perfusion as a hepatic assist in acute liver failure demonstrates no significant advantage of this approach over conventional intensive care therapy³⁵. Similarly, no significant benefit has been demonstrated in the randomized control trial of the HepatAssist bioartificial liver unit³⁶.

Clinical trials of cellular xenotransplants have included injections of porcine pancreatic islet cells in insulin-dependent diabetic patients^{37,38,39,40,41,42}, baboon HIV-resistant haematopoietic cells to treat a patient with AIDS⁴³, encapsulated chromaffin cells from newborn calves to treat chronic pain⁴⁴, and porcine neural cells for the treatment of patients with Parkinson's disease^{45,46,47}, Huntington's disease⁴⁸, epilepsy and stroke^{49,50}. Additionally, an estimated 1,000 burn patients have been treated with autologous skin cells, which are also considered a type of xenotransplantation because they were grown on mouse feeder layers⁵¹. The most encouraging results are found in cellular xenotransplants for the treatment of diabetes, chronic pain and Parkinson's.

4.2 Biological barriers to clinical xenotransplantation

4.2.1 Immunological incompatibility

As evident from the many dismal attempts in the past, whether xenogeneic cellular, tissue and organ grafts may constitute a future replacement for human grafts, depends in the first place on whether the tissue will be sufficiently tolerated by the human immune system. The incompatibility of cross-species grafts causes more intense and challenging immunological reactions than grafts transplanted between humans and continues to inhibit

effective clinical use of most xenotransplantation applications⁵². The precise mechanisms that underlie xenograft rejection were not known at the time the first organ xenotransplants were performed (in fact, at the time of Jaboulay's first attempts, Karl Landsteiner was still studying the ABO system of blood groups⁵³) and remain incompletely understood to date. Nevertheless, some level of interspecies immunological incompatibility had been indicated since the beginning of the 19th century. In 1816 and 1818, respectively, John Henry Lealock and James Blundell demonstrated from various cross-species animal transfusion models that donor and recipient must be of the same species. In 1863 Paul Bert published 'On animal transplantation', a doctoral thesis in which he demonstrated that blood could be successfully cross-circulated between two rats but not between a rat and a pig. In his recommendations, he noted that transplantations between different species, particularly between an animal and a human, should be avoided⁵⁴.

Xenotransplantation research has not only persisted despite that early recommendation, it has heightened the immunological challenge by choosing an evolutionary disparate species as the source animal. As mentioned above, throughout the history of xenotransplantation, a number of source species have been considered, amongst which the primate has shown to provide the best results. Most recently, tilapia fish have been proposed as a source of pancreatic cells and both mouse and insect cells have been used to generate human cells in culture⁵⁵. Nonetheless, it is generally agreed that the pig is currently the most preferred source animal for most replacement cells and all organs. The primate is considered an inappropriate source of xenografts due to both practical and ethical considerations (which will be addressed in the following section). The evolutionary distance between pigs and humans, however, gives rise to greater physiological and biochemical incompatibilities and causes destruction of the xenograft within minutes to hours after transplantation. The most problematic barriers do not involve responses to antigen incompatibilities in blood groups, as is the case in allotransplantation. While the antigen expression of pig blood groups is comparably weak as it is, herds of pigs have even been created which carry the universal donor blood type O⁵⁶. Rather, the most drastic phase of xenogeneic rejection is due to a natural immunological response that developed millions of years ago to offer protection against intruding microorganisms⁵⁷.

Hyperacute rejection

Hyperacute rejection occurs when a transplant between discordant (widely divergent) species elicits natural antibodies, known as 'xenoreactive natural antibodies', which target

the species-specific donor tissue. In the early 1990s it was discovered that pig-to-human transplants evoked human xenoreactive antibodies against a sugar molecule called galactose-(α 1-3)-galactose (Gal α 1-3Gal) that is present in the lining of porcine blood vessels⁵⁸. This carbohydrate is expressed by many animal species, but humans, apes and Old World monkeys have lost the capacity to produce it in the course of evolution⁵⁹. As a result, our bodies produce natural antibodies to the antigen as a protection mechanism. Indeed, the Gal sugar molecules are also found on the surface of certain bacteria, viruses and parasites. It is known that at least 85 per cent of human xenoreactive natural antibodies are targeted specifically to Gal α 1-3Gal⁶⁰. The impact of xenoreactive natural antibody activation is profound. When the human immune mechanism comes into contact with a porcine vascularized xenograft, the organ turns into a black, swollen and mottled mass within several minutes or hours. The circulating natural antibodies quickly bind to the Gal α 1-3Gal and activate a destructive succession of nearly three dozen proteins, which is known as 'complement'. The process starts with damaging, and often destroying, the endothelial cells that compose the cell lining of the cavities of the heart and blood/lymph vessels. Consequently, the process of blood coagulation (for example, clot formation in the blood) is initiated, causing thrombosis, which in turn obstructs the xenograft and surrounding tissues from sufficient blood flow. Ultimately, the damages in the endothelium result in the exposure of the underlying matrix, the breakdown of metabolic and oxygen pathways and the rapid death of the recipient. Hyperacute rejection develops in all organ xenotransplants between discordant species, but does not pose as much of a problem for cell or tissue xenotransplantation.

Hyperacute rejection can be overcome if we can circumvent the binding of the antibodies to the Gal sugar by either eliminating the xenoreactive natural antibodies or by inhibiting complement. Advances in this area have come up with a range of possible strategies and no longer render this form of rejection the major obstacle to xenotransplantation in pre-clinical models. Importantly, however, this progress led to the understanding that hyperacute rejection is only one of several rejection processes that inevitably develop within days after transplantation.

Subsequent rejection phases

Acute vascular rejection occurs over days to weeks and, although the exact biology is not fully understood, also consists of the progressive destruction of the pig blood vessels. It appears as a delayed form of hyperacute rejection (and is sometimes also referred to as

‘delayed vascular rejection’) as it involves persistent attacks of xenoreactive antibodies. Nevertheless, it has been shown that it is a different process and that xenoreactive antibodies trigger it⁶¹. Those anti-donor antibodies play the most significant part in the rejection process, but certain white blood cells, such as T lymphocytes (‘killer cells’) and macrophages, are also involved. Acute vascular rejection damages the inner layer of the coronary arteries, and may result in scarring, endothelial cell swelling and activation and a decrease in blood flow⁶².

Acute cellular rejection progresses over weeks or months after xenotransplantation and resembles the immunological reaction that occurs after allotransplantation. The process generally involves the destruction of the xenogeneic epithelial cells, which are responsible for the function of the transplant tissues. The attack is predominantly generated by host T lymphocytes that intrude the xenograft and directly attack its cells (hence, the term ‘cellular rejection’). T lymphocytes play a major role in fighting infection and are capable of ‘memorizing’ the antigens they have detected, allowing for a quick response when the antigen is re-introduced. This type of rejection has not presented a major barrier to the survival of pre-clinical xenotransplants, but that may be the effect of the use of high and clinically intolerable doses of immunosuppressive drugs.

Chronic rejection may take many months or years. Due to the limited survival obtained to date, it has not been widely observed in xenotransplantation experiments. It is however the major constraint to long-term success in allotransplantation. The process is poorly understood but may result in the narrowing of blood vessels to the extent that the attached tissue is starved of essential nutrients.

4.2.2 Host or source animal manipulations

In order to circumvent the various stages of rejection, pig-to-human immune compatibility must be enhanced either by manipulating the prospective source animal and/or its grafts, or by suppressing the immune system of the recipient prior to xenotransplantation.

Source animal modifications

Genetic manipulations of the source animals have provided the most successful strategies for circumventing hyperacute rejection in pre-clinical models. In this sense, and in

comparison with nonhuman primates, pigs are a particularly rewarding species given the relative ease with which they can be genetically manipulated to express extrinsic genes⁶³. The procedures involve manipulating the pig's genome so that the animal's cells, tissues and organs are partly 'human' - or, at least, recognized as such by the human patient's immune system.

Transgenic pigs The first successful approach to counter anti-Gal antibody mediated complement activation consisted of genetically engineering pigs to express human complement regulatory proteins⁶⁴. The rationale underlying this approach is that the human complement-regulatory proteins will be able to protect better against human complement. Over the past decade, several strains of transgenic pigs that express one or more human complement regulatory genes have been bred. The first transgenic pig was born on 23 December 1992 after injection of a small amount of human DNA into fertilized sow eggs⁶⁵. 'Astrid', as the resulting piglet was named, expressed human decay-accelerating factor (hDAF). In 1995 transgenic pigs were produced which expressed both the hDAF and CD59 human complement regulatory proteins⁶⁶. When transplanted into baboons, such transgenic grafts provided survival advantage over wild-type pig grafts of up to 30 hours⁶⁷. Wild-type pig grafts were typically hyperacutely rejected in less than 80 minutes. Life-supporting ('orthotopic') hearts obtained from hDAF transgenic pigs have since achieved survival of a month in nonhuman primates⁶⁸. Life-supporting transgenic renal xenografts have obtained a maximum survival time of 78 days⁶⁹. In baboons, the transgenesis has effectively down-regulated activity of the complement cascade without any form of immunosuppression⁷⁰. The continuous development of multi-transgenic pigs has shown to provide even greater protection against human complement-mediated damage^{71,72}. These more advanced genetic manipulations of the pig genome into offspring have been facilitated by the development of somatic cell nuclear transfer (cloning) technology in pigs, with the first cloned pigs born on 5 March 2000⁷³. Nonetheless, even when hyperacute rejection is avoided, the hDAF transgenic organs transplanted into nonhuman primates eventually undergo a rejection process that mimics acute vascular rejection.

GalT-KO pigs The introduction of the technique of nuclear transfer in pigs soon allowed for an alternative source animal modifications to prevent hyperacute rejection. The technique consists of 'knocking out' the gene for α 1,3-galactosyltransferase in order to avoid synthesis of Gal α 1-3Gal. The production of cloned piglets that lack one allele of the gene - 'Gal-T knockout (GalT-KO) pigs' - was reported in 2002 by two independent research

teams^{74,75}. Shortly after, in August 2002, PPL Therapeutics announced the production of the first double knockout piglets, which lack both copies of the $\alpha 1,3$ -galactosyltransferase gene⁷⁶. GalT-KO pigs have allowed for further increase in survival rates in xenotransplantations of hearts and kidneys to primates in comparison with the use of hDAF pigs. *In vivo* results of a non-life supporting ('heterotopic') heart transplant in a pig-to-baboon model obtained maximum graft survival of 179 days, the longest survival recorded of pig-to-nonhuman-primate organ transplantation to date^{77,78}. In non-life-supporting (heterotopic) transplants, the native organ is kept in place and the xenogeneic organ is transplanted in a different location within the body. Life-supporting xenotransplantation of a GalT-KO kidney resulted in survival of more than 80 days in nonhuman primates with no evidence of rejection⁷⁹.

Both strategies, especially when combined, are effective measures against hyperacute rejection. Further improvement of survival seems likely, provided that progress in site-specific genetic and transgenic modifications continues. Nonetheless, the human host may still not tolerate the xenografts as well as the allografts with conventional immunosuppressive regimens⁸⁰.

Transfer of human stem cells or primordia into developing animals should also allow for the creation of 'humanized' grafts. Preliminary experiments have been conducted to generate animal grafts that express a significant amount of human cells⁸¹. Almeida-Porada *et al.* injected human stem cells in developing sheep and found that the human cells contributed to the sheep's blood, bone, liver, heart and nervous system⁸². Others have established the differentiation of human stem cells (derived from bone marrow) into human chondrocytes, adipocytes, myocytes, cardiomyocytes, bone marrow stromal cells and thymic stroma⁸³. The human cells persisted in the xenogeneic sheep environment for up to 13 months. Ultimately, the hope exists that use can be made of a patient's own stem cells. If these cells were to be injected into developing animals, the animals may, once born, express a sufficient amount of that patient's cells in the grafts required. The genetic similarity between host grafts and recipient would thereby dismiss major immunological incompatibilities. The use of an animal 'host' as a growth environment for human embryonic developing organ primordia, as mentioned in the previous chapter, is also promising. The advantages of that approach include the fact that early staged organs, obtained at the proper time during embryogenesis, automatically differentiate into the desired tissue and facilitate vascularization. Furthermore, pre-clinical data suggest that kidney and pancreatic primordia can be effectively transplanted across both concordant

(rat to mouse) and highly discordant (pig to rodent) xenogeneic barriers⁸⁴. Nonetheless, the success of the pre-clinical studies in large animal models has been constrained by the failure to identify the optimal gestation time for transplantation into the animal host environment⁸⁵. Moreover, it will be essential that the embryonic organs do not come into contact with the host antigens. Such contact could cause the production of epitopes and thereby elicit an immune response.

Immunoisolation by encapsulation of transplanted tissue appears to be a particularly feasible approach to avoid rejection in cellular xenotransplantation. The procedure consists of encapsulating cells or small tissues in a semi-permeable membrane that cannot be penetrated by destructive factors but does facilitate two-way diffusion of nutrients from the host circulation and desired products from the xenograft. Alternatively, the xenogeneic cells or tissues are placed in a tubular scaffold that becomes subcutaneously covered with connective tissue (collagen) from the recipient. The effectiveness of porcine neonatal islet immunoisolation was suggested by reports of long-term reversal of diabetes in nude mice and normalized blood glucose levels in diabetic monkeys for up to 803 days⁸⁶. Clinical transplantation of encapsulated *human* islets resulted in insulin independence for more than nine months in one diabetic patient⁸⁷. The technique appears to improve survival rates of *xenogeneic* islet cells transplanted in humans as well. Whereas the first trial of porcine islet xenotransplantation in 1994 showed no improvement in the patient's insulin requirement⁸⁸, a recent attempt using encased porcine islet and Sertoli cells (the latter which have been found to consist of an immunomodulating factor) appears encouraging⁸⁹. At follow-up four years after the xenotransplants, 50 per cent of the human recipients (n=12) had a significantly reduced insulin requirement; two patients had achieved temporary insulin-independence. However, it is important to note that these results are not uncontested (we will address this further in the General Discussion).

Xenograft recipient modifications

As an alternative to source animal modifications, the immunological incompatibilities between pig and human may be decreased or suppressed by modifications in the potential recipient prior to a xenotransplantation.

The most obvious approach would be the use of immunosuppressive drugs similar to those applied in the field of allotransplantation. Unfortunately, the therapies that generally suppress the immune response in allotransplantation are not aggressive enough to counter

rejection of nonhuman animal grafts. Adapted regimens would be highly toxic and are not clinically tolerable at the present time. While research into drugs that avoid the activation of complement and blood coagulation persists⁹⁰, it is unlikely that those drugs will provide long-term solutions.

Initial strategies to prevent hyperacute rejection aimed at diminishing the presence of xenoreactive antibodies. In 1966 Perper and Najarian first attempted that approach pre-clinically by perfusing the prospective recipient animal's blood through the kidneys of source animals. Later techniques involved the use of plasmapheresis and, more recently, specific depletion of xenoreactive antibodies has been achieved using affinity columns that bear Gal α 1,3Gal. Depletion of xenoreactive antibodies using immunoabsorption columns, in conjunction with plasmapheresis and immunosuppression, has also countered acute vascular rejection. Another method to prevent hyperacute rejection was the administration of cobra venom factor to activate complement so that it would be consumed by the time the grafts are transplanted. Other agents are being considered as means to 'interrupt' the complement cascade⁹¹.

Ideally, however, the recipient should be altered so that the immune system completely, and permanently, tolerates the foreign graft. That state, known as 'immunological tolerance', is the destination of further allotransplantation research as well. Described as 'the immunological holy grail'⁹², tolerance is a condition in which the immune system tolerates specific donor cells, tissues and organs as if they were its own, but remains responsive to other invading microorganisms. It would completely alleviate the need for any additional immunosuppressive therapy. Apart from the medical utility associated with drug independence, tolerance may be the *only* chance for long-term effective discordant xenotransplantation.

Various approaches to induce immunological tolerance exist, including haematopoietic stem cell transplantation, transplantation of porcine thymus tissue (part of the immune system which generates T-cells), molecular chimerism using a gene therapy approach and temporary depletion of T-cells or induction of T-suppressor cells⁹³. Early efforts to induce tolerance in animal models mainly consisted of introducing species-foreign cells into foetal animals before their immune system was (fully) developed. While it could theoretically be feasible in humans as well, that method is not practicable. There are severe ethical barriers against creating human embryonic cross-species chimeras and potentially harmful effects of introducing porcine cells on further embryonic development are unknown.

Importantly, moreover, as it is not predictable which fetuses will need a transplant in the future, that approach would require that all fetuses carried to term should be sensitized to porcine cells⁹⁴. Alternative approaches primarily involve the temporary destruction of the host's immune system (for instance, through radiation of T lymphocyte regulators or whole body irradiation) so that it will renew itself only after transplantation of foreign cells, allowing for the co-presence of both recipient and donor (most commonly, bone marrow) cells. Those techniques are not without risk for patients and have produced rather disappointing results in terms of persistent anti-pig antibody production⁹⁵. The failure to overcome returning antibody production has also been observed after thymic transplantation⁹⁶, xenoreactive antibody depletion⁹⁷ and molecular chimerism, in which animal genes instead of cells are transplanted in the immunosuppressed host⁹⁸.

4.2.3 Physiological incompatibility

While the feat of human tolerance to xenografts still lies ahead, long-term success of pig-to-human transplants is also left wanting by other potential incompatibilities between the species. Those incompatibilities can manifest themselves in differences on physiological, homeostatic, metabolic and hormonal levels and remain largely unexplored.

The major disparities between human and porcine physiology that have been identified so far include differences in haematology, enzymes, hormones and liver metabolism. Sufficient resemblances in terms of growth factors and substance supply, control and transport are crucial for the integration of solid organ xenografts in a host environment. Theoretically, incompatibilities in growth hormone could produce over- or undersized growth of the xenotransplant. Illustrative in this respect is the production of giant mice after insertion of bovine or porcine growth hormone gene in its genome. However, as pertains to known differences between human and pig growth hormones (by up to 19 per cent), no severe incompatibilities are expected⁹⁹. Indeed, miniature swine breeds have been identified which provide organs that, in comparison with other species, best approximate adult human size. Of persistent concern, by contrast, is the fact that the specific carrier molecules that transport substances such as hormones throughout the body, are species-specific. Furthermore, the levels of circulating electrolytes, sugars and other biochemical products maintained by organs may also vary between pigs and primates. The disturbances in haematology are of most concern. Many coagulatory disturbances have been indicated in various pig-to-nonhuman-primate xenotransplants¹⁰⁰

and pose an increased risk of bleeding disorders and vascular thrombosis¹⁰¹. Adverse clotting may contribute to xenotransplant rejection and problems related to circulation incompatibility may inhibit the delivery of oxygen and nutrients and removal of waste substances¹⁰². Differences between humans and pigs have also been found with regard to haematocrit, blood composition, blood viscosity, red blood cell surface area and diameter - all of which may contribute to a weak integration of the xenograft in human microenvironments.

Due to the horizontal posture of pigs, concern has also raised about incompatibilities of the heart in terms of heart valve size, pulmonary circulation, and other physiologic functions¹⁰³. However, postural changes do not appear to affect the function of porcine hearts - nor of lungs and kidneys for that matter - when transplanted in nonhuman primates¹⁰⁴. In fact, of all solid organ xenotransplants, the heart appears to be the least susceptible to major physiological incompatibility problems. Concordant monkey-to-baboon cardiac xenotransplantation has achieved the longest survival rates ever recorded in the history of xenotransplantation (up to 540 days)¹⁰⁵. In a cautious note, however, it must be added that improved survival of transplants between more disparate species may reveal important anatomical differences with regard to innervation of the heart¹⁰⁶. In comparison, the increased survival rates achieved after transplantation of transgenic porcine kidneys into nonhuman primates have allowed for a more detailed study of the physiological effects of discordant kidney xenotransplantations. It has been suggested that porcine erythropoietin, a hormone that is responsible for the control of normal blood cell production in the bone marrow, will not function in humans because primate erythropoietin receptors do not recognize the pig version¹⁰⁷. Cross-species transplantation of the liver has also expressed significant species-specific differences, particularly in respect to the structure and composition of transport proteins such as serum albumin¹⁰⁸. Further investigations to assess the extent to which pig livers can maintain normal human homeostatic mechanisms, are required. The level of physiological compatibility between human and porcine lungs is currently the least understood, since porcine lung xenotransplants have not sustained survival of nonhuman primates beyond a few hours¹⁰⁹.

While the biological barriers to solid organ xenotransplantation remain substantial, various cellular replacements prove to be more compatible with the functions of the native cells. Pig islet cells provide adequate blood levels of glucose in humans. Moreover, while xenogeneic islet transplantation is known to initiate an immediate inflammatory reaction in human blood, which causes coagulation, that effect appears to be manageable by

appropriate drug regimens¹¹⁰. Porcine neural cells are also a good match in terms of structure and function. Various animal studies have provided proof of principle that xenogeneic neural tissue can survive and function and that it can reduce the symptoms of neurodegenerative disease. The studies even suggest that the level of neural cell migration, innervation and integration is better compared to equivalent allografted tissue^{111,112,113}. The first neural xenograft survival in the human brain was documented in 1997¹¹⁴. Embryonic pig cells had been implanted into a patient with Parkinson's disease and were found to have generated pig dopaminergic and other neural cells. The neurons had grown axon extensions into the host brain and evoked only low reactivity from human microglia and T-cells. Nonetheless, while some neurons survived over seven months, large numbers of dopaminergic neurons had only poor graft survival. A different study, three years later, reported follow-up results one year after the successful transplantation of embryonic porcine ventral mesencephalic tissue in twelve Parkinson's patients¹¹⁵. The results showed that the tissue was well tolerated without serious adverse effects. Overall rates of Unified Parkinson's Disease Rating Scale scores improved by 19 per cent and three patients, who had received particular immunosuppressive regimens including cyclosporine, improved over 30 per cent. Those results are similar to the initial experience with unilateral human embryonic allograft transplantation, although in the latter case much less cells are transplanted (in this study, 12 million embryonic pig neurons were transplanted!). Apparently, although the immune rejection in the brain is thought to be rather weak, most of the xenografts nevertheless undergo rejection for lack of proper protection measures. Defining the optimal environment for long-term neural cell growth and the appropriate concentrations of cells also remains a challenge¹¹⁶. Again, it must be noted that many of the specific physiologic problems associated with each type of xenograft, cannot be conclusively identified until substantially longer graft survival rates are achieved in nonhuman primates and humans.

4.3 Restricting the emergence of xenogeneic infectious disease

Although significant progress has been made in the understanding and approach of immunological and physiological incompatibilities, it is clear that many challenges remain to be met before xenotransplantation, of organs in particular, will be a viable routine therapy for waiting list patients. Precisely at what point pre-clinical efficacy is sufficient to warrant clinical applications in humans is, however, unclear. In 2000, the Xenotransplantation Advisory Committee suggested that trials of cardiac and lung

xenotransplantations should be considered when approximately 60 per cent of primates survive life-supporting pig organ transplants for at least three months¹¹⁷. The Spanish Xenotransplantation Commission suggested survival and proper function of the grafts for at least six months in nonhuman primates¹¹⁸. In comparison with the start of allotransplantation, those are rather demanding requisites. Norman Shumway, for instance, felt that survival for 4 to 21 days among 85 per cent of dog recipients of cardiac transplantation was sufficient to warrant the move to clinical trials¹¹⁹. The argument could be put forward that, in a situation where a patient is sure to die soon without a transplant, even the most extreme operative mortality rate is acceptable. It has also been noted that the pre-clinical survival rate requirements should distinguish between the various types of xenografts. In this sense, perhaps, short survival rates of xenogenic cellular xenotransplants may be acceptable to warrant further progress in clinical research, provided that the graft malfunction is not dangerous for the patient. Nevertheless, currently, authorized xenotransplantation trials of whichever type of xenograft are extremely rare. The major brake on further progress is clearly related to the possibility that xenotransplantation may facilitate adverse effects to third parties not involved with the potential clinical benefits. The concern has been raised that infectious agents derived from animals may be transferred along with the xenograft and endanger public health.

4.3.1 Contemporary relevance

The distress over the risk of unleashing infectious epidemics, or at worse pandemics, from exposure to animal material could not be more topical. At the time of writing, daily news reports detail the cautious measures being undertaken to prevent a further outbreak of avian influenza A/(H5N1). That strain is highly contagious to all bird types, although not all infected bird types show symptoms of infection. Most bird species, such as domestic poultry, rapidly develop fatal disease. The spread of the virus is striking. The virus has affected poultry in a surface area extending from south-east Asia to parts of Europe¹²⁰. Although influenza viruses are normally highly species-specific, this particular strain has also caused human infection and severe disease. Importantly, of all avian influenza strains viruses that have been transmitted to humans throughout history, H5N1 has resulted in the greatest number of human deaths. On 21 February 2006, and since the start of the current outbreak in December 2003, 340 human cases of avian influenza A/(H5N1) and 184 deaths were confirmed¹²¹. The WHO describes the situation as a phase 3 (out of 6) of pandemic alert: the virus subtype is transmitted to humans, but has not yet endured spread among

humans¹²². Nevertheless, the risk that the H5N1 virus - if given enough opportunities - will develop the characteristics it needs to start a human influenza pandemic is of greatest concern. The relevance of the concern lies in the fact that a wide range of human diseases have been acquired through the transmission of viruses, bacteria, or prions from an animal to a human (zoonosis) throughout history. The best-known example is the Human Immunodeficiency Virus (HIV). Compelling evidence exists that a simian variant (SIV) from sooty mangabeys is the recent ancestor of HIV-2 and that SIV from chimpanzees is the predecessor of certain types of HIV-1¹²³. New zoonoses have emerged particularly in the last fifteen years, and are estimated to make up 75 per cent of all emerging infectious diseases¹²⁴. Examples include Ebola, Creutzfeldt-Jakob disease, rabies, West Nile virus, Nipah, Hendra and Menangle viruses, Hantavirus, monkey pox and Severe Acute Respiratory Syndrome (SARS). Transfer of zoonosis may occur through either direct contact (for instance, through a bite from an infected animal) or indirect contact (for example, through the consumption of contaminated food)¹²⁵. Threats have emerged from both exotic hosts (cf. Ebola) and domesticated animals (cf. the new variant of Creutzfeldt-Jakob disease emerged from cattle herds in the UK). Various situations may give rise to new infections, but current ecological and microbiological aspects enhance the possibilities. Previously unrecognized infections often appear as a result of ecologic transformations and anti-microbial resistance developing in existing agents¹²⁶.

4.3.2 Xenozoonosis

Hypothetically, xenotransplantation could allow transmission of zoonosis along with the xenograft (xenozoonosis) and contamination could extend beyond the individual transplant patient, to their intimate contacts, health care workers and the public at large. Despite the long history of attempts at xenotransplantation, serious concern regarding the public health hazard materialized particularly in the second half of the 1990s. Arguably, that is due to improved understanding of and sensitivity towards zoonotic disease, a looming threat of biological terrorism and the potential for rapid, global spread of infectious disease through mass air travel. The urgency to establish rigid regulations so to protect the public from xenogeneic infection was particularly felt in the United Kingdom, which had just experienced the crisis over BSE¹²⁷. In October 1999 the UK became the first nation in the world to adopt a formal regime of preventive measures against xenogeneic virus transfer. Specific regulation with regard to xenotransplantation public health risks initiated with the launch of an Advisory Group on the Ethics of Xenotransplantation near

the end of 1995. In its report to the British Health Department, published in 1997, several detailed conditions for further xenotransplantation research were stipulated¹²⁸. The group requested the establishment of a regulatory body to oversee national development of xenotransplantation. That resulted in the creation of the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). While the US had initially authorized local hospital review committees to approve all clinical xenotransplantation investigations, the US Public Health Service also felt the need to optimize the protection of public health and requested a central control mechanism in 1996¹²⁹. As a result, the Secretary's Advisory Committee on Xenotransplantation (SACX) was set up to serve as the national authority over all aspects concerning the scientific development and clinical application of xenotransplantation (although it has by now been disestablished due to the low xenotransplantation activity). Governmental advisory commissions have since been set up in Canada, France, Germany, Spain, Sweden, the Netherlands, Australia and New Zealand.

One of the important recommendations made by the Advisory Group on the Ethics of Xenotransplantation (and subsequently adopted by the UKXIRA and the US Food and Drug Administration (FDA)¹³⁰) was to preclude the use of nonhuman primates as xenotransplant source animals due to the genetic proximity between humans and nonhuman primates. The increased likelihood of virus transfer from nonhuman primates was suggested by the global spread of HIV-1 and contamination of simian virus in early poliovirus vaccines in the 1950s¹³¹. The dangers specific to primate-to-human xenotransplantation have indeed been affirmed: a postmortem blood analysis of a baboon liver recipient indicated infection of simian cytomegalovirus infection¹³².

The subsequent use of pigs as source animals caused less theoretical concerns regarding transmission of novel pathogens. Pigs have lived in domestication with humans for thousands of years and diagnostic tests and husbandry practices are capable of reducing many of the infectious risks we have come to know since. However, a new *de facto* moratorium on clinical applications of xenotransplantation came in 1997 after the discoveries that porcine endogenous retroviruses (PERVs) were able to infect human primary cells and cell lines *in vitro* and could adapt to those cells by serial transmission on uninfected cells^{133,134}.

Species-specific endogenous retroviruses are present in the DNA of all mammals adequately studied to date, including humans. As such, and in contrast to exogenous

retroviruses, endogenous retroviruses are integrated in all cells of the host body, and thus difficult to exclude. Although the viruses are no longer capable of causing active infection in their native host, they may induce infection upon transfer to another species - as is illustrated by the transfer of HIV through non-pathologic simian carriers. To this day, the risk of creating a xenotransplant related epidemic, or at worse pandemic, remains unquantifiable. No PERV-related disease has been shown to occur in humans to date and there is no way of estimating the risk of infection. Nevertheless, a cautious approach is supported by the fact that precisely viruses that persist asymptotically in quiescent or latent phases, constitute the greatest hazard to public health. Those viruses can hypothetically spread easily without being noticed. Moreover, the severity of the danger of PERVs is emphasized in light of known homology to other retroviruses, such as feline leukaemia virus (FeLV) or murine leukaemia virus (MuLV), which induce tumours or immunodeficiency in the infected host¹³⁵. Furthermore, the risk of virus transfer is enhanced by the fact that transplantation bypasses most of the patient's usual protective physical and immunological barriers and due to lack of knowledge about the behaviour of source animal-derived infectious agents in immunosuppressed humans.

4.3.3 Regulatory constraints to clinical applications

Evidence of PERV infections *in vitro* and fears that there may be other, undiscovered transmissible agents compelled several pleas for a moratorium on clinical xenotransplantation^{136,137,138}. Currently, public consultations in Norway, the Netherlands, New Zealand, Australia and Canada have resulted in the conclusion that xenotransplantation should not start in those nations until critical safety issues are resolved. In most nations, however, between 1997 and 1999 a temporary *de facto* moratorium in name of the precautionary principle has been replaced by tighter national oversight. Although that oversight is rarely embedded in a legal framework specific to xenotransplantation, various regulatory and advisory authorities have published detailed safety protocols for xenotransplantation research and clinical trials. The protocol review pertains to the procurement and screening of source animals, the clinical and pre-clinical testing of xenotransplantation products and the post-xenotransplant monitoring/surveillance of recipients. The following is a summary of the most significant requirements as stipulated in the latest guidelines provided by the US Food and Drug Administration (FDA)¹³⁹ and Public Health Services (PHS)¹⁴⁰, the UKXIRA^{141,142,143}, the Council of Europe Committee of Ministers (COECM)^{144,145}, the European Agency for the Evaluation of

Medical Products (EMA)¹⁴⁶, the Organisation for Economic Co-operation and Development (OECD)^{147,148} and the World Health Organization (WHO)^{149,150}.

Xenotransplant source animal screening

As a precondition for appropriate source animal health status, the animals must be derived from closed herds with documented health screening programs. The prospective source animals should be bred and housed in barrier facilities that are free of designated pathogens. No natural, non-sterile feeds should be used. Specified protocols for monitoring and diagnosing disease and infectious agents in the herd should be in place. Source animals should be screened for a list of infectious agents as generated by experts on infectious diseases of the species involved. Special consideration should be given to infectious agents known to infect the source animal, known to cause zoonoses, or known to occur in latent state. In addition, general assays for recognition of classes of agents should also be applied. Biological specimens should be routinely collected and tested for infectious agents by appropriate assays. Those samples must be archived for future purposes to facilitate identification of infections after the grafts have been retrieved and/or transplanted (the recommended durations of storage range from 20 to 50 years). In addition, detailed information concerning the health status of the source animals - including all illnesses, treatments, drugs and medical care involved - should be documented consistently. Several weeks prior to harvest of the grafts, the individual source animals should be quarantined and screened extensively. Transportation of source animals should be avoided if possible. Postmortem, the animals must not enter the food/feed chain. Special care should also be taken to monitor the health of humans who are in regular contact with the animals. All animal caretakers must minimally consent to the procurement of baseline samples. Additional screening may include periodic sampling and storage of serum or plasma.

All pre-clinical xenotransplantation studies must comply with the monitoring procedures of source animals intended for use in clinical trials. Human cells that have been co-cultured with nonhuman animal cells (such as embryonic stem cells derived from murine feeder layer cells) are also included in xenotransplantation regulation, but require less detailed documentations of the health status of source animal colonies.

Xenotransplant product screening

Once the xenografts are retrieved from the source animal, additional efforts must be conducted to analyze and record the safety status. Stringent sterility requirements apply in every step of the process. For those grafts that must be transplanted immediately upon retrieval, the screening should be conducted on biopsy samples. For cells and tissues that are stored, processed, or expanded before transplantation, further research should specify the identity, purity and potency of the active components. Appropriate procedures for inactivation or removal of infectious agents should be developed and applied. Extra efforts may be required to differentiate newly emerging viruses or viruses for which specific assays have not yet been developed. Samples of all xenografts and/or products derived from xenografts should be cryo-preserved and archived for further testing.

Xenotransplant recipient screening

The greatest challenge in addressing the risk of infectious disease during clinical applications of xenotransplantation, is the need to assure the safety of the recipient's contact populations. They include close contacts - such as family, friends, and health care providers - as well as the community at large. In response to the public health threat, the guidelines restrict clinical xenotransplantation to those transplantation centres that have sufficient know-how to test for potentially causative xenogeneic infectious agents *in vitro* and *in vivo* or that have established collaborations with relevant experts. The tests should enable the identification of latent infectious agents and should be adapted to recognize new pathogens as well. Diagnostic testing should not be limited to the event that the recipients show indications of disease, but will continue with decreasing frequency throughout the lifetime of the recipients even when he or she is asymptomatic. Lifelong surveillance programs require the repeated procurement, laboratory analysis and long-term conservation of biological specimens in order to detect potentially latent viruses. The screening will continue postmortem with autopsy and extensive histopathological assessments of all samples and cultures of the recipient. All data collected during follow-up must be available for investigation for up to fifty years after the transplant. Throughout that process, all adverse events must be recorded and reported. Identification of a potentially hazardous infectious agent calls for instant notification of the relevant health authorities.

Long-term medical monitoring is applicable even if the clinical trial fails to obtain sufficient graft survival. The consenting trial participant loses his or her right to withdraw from the experiment ('imposed extended compliance'). In case the participant fails to comply with the constraints associated with xenotransplantation, public health authorities may, if necessary, force compliance. The recipient should consent to the potential need for confinement or specialized medical housing. Current and future close contacts should also be notified of the infection risk and will also be asked to take appropriate measures to restrict exposure to others. Close contacts are generally defined as those persons who bear the risk of intimate contact with the xenotransplant recipient's bodily fluids (including blood and saliva). The prospective recipients are responsible for taking appropriate precautions for sexual and non-sexual contact. They and their intimate contacts will be precluded from donating blood, ova, sperm, or any other body parts for use in humans.

The recipient has the responsibility to ensure traceability of his or her whereabouts and must inform the medical team of possible changes of address. Various nations are developing computerized registers of all xenotransplant product recipients in order to facilitate the tracking process. Maintaining biological specimens in a central archive or in an interactive network should also facilitate rapid detection of infectious disease. Although the data of the patients should be managed in accordance with the principle of confidentiality, this principle may be breached if the immediate interest of public health is at stake.

Unless very high assurance of safety can be verified, the initial trial participants will most likely be patients with serious or life-threatening diseases for whom appropriate alternative therapies are lacking. Given the stringent public health measures, the prospective recipients must be screened to assess the likeliness of long-term lifestyle requirement compliance. Only in desperate situations, and when there are sufficient scientific indications to anticipate a life-saving benefit, should patients incapable of giving informed consent (including incompetent children) be considered as potential recipients.

Global public health surveillance

In 2000 the Council of Europe's Working Party on Xenotransplantation conducted a survey of the legal and regulatory frameworks relevant to xenotransplantation within 27 states¹⁵¹. While 80 per cent of the responding nations of the states required that specific authorization should be obtained before clinical trials on humans are conducted, only 26

per cent had a specific framework to deal with clinical xenotransplantation protocols. Only 36 per cent had guidelines for clinical xenotransplantation application. A mere 26 per cent had established measures to respond to a xenogeneic infectious outbreak. In the understanding that the risks of xenogeneic virus are not confined to the nation in which an outbreak initially occurs, the COECM, WHO, EMEA, OECD and the International Xenotransplantation Association (IXA) have emphasized the need to establish transnational harmonization of accepted norms for xenotransplantation surveillance. The recommendations specify that clinical applications of xenotransplantation cannot be carried out without effective national regulatory control and surveillance mechanisms and/or without specific authorization. Additionally, they mandate rapid collection, evaluation and communication of relevant data on a global scale through the development of international or interconnected database registries. Adverse effects of a xenotransplantation must be reported proactively to the national public health authorities of other states concerned. A system for international, cross-border tracking of the recipients should be installed and protective measures to prevent secondary infection should be standardized.

4.4 Conclusion

Xenotransplantation stands ‘the test of time’ in terms of the persistent pursuit of that approach to alleviate various human diseases for which human donor grafts are currently lacking. However, with regard to the short survival rates obtained in solid organ xenotransplantation, it clearly fails the test of time in order to be established as an effective therapy. It remains to be seen whether and, if so, when further progress in immunology and physiology will provide adequate xenograft survival in humans. For now, imminent xenotransplant trials are limited to direct implantations of porcine cells for the treatment of liver failure, diabetes, and neurological disorders¹⁵². In retrospect to the introductory quote, it is noteworthy that various regulations have been put in place to control but not immobilize further xenotransplantation research all together. The remaining part of this thesis is contributed to an analysis and evaluation of the ethical issues that have arisen along with the development of xenotransplantation.

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PART THREE

THE PIG - THE OTHER VICTIM?

5 To the core of porcine matter: questioning the inherent immorality of producing transgenic pigs for xenotransplantation

Adapted from: Ravelingien A, Braeckman J. To the core of porcine matter: questioning the inherent immorality of producing transgenic pigs. *Xenotransplantation* 2004; 11: 371-375.

Abstract

The production of transgenic pigs for xenotransplantation is based on an urgent human need for transplantable organs. Although the particular genetic modifications are small and do not alter the organism phenotypically, several authors consider it morally problematic. This chapter attempts to establish whether there are genuine reasons to refrain from producing ‘humanized’ pigs for xenotransplantation. We distinguish two types of ethical arguments often confused in debating the matter: consequentialist and inherent arguments. Whereas the first type of argument pertains to the potentially negative effects of the procedure, the second type claims that genetic engineering of animals is ‘inherently’ wrong; that the action itself - regardless of the effects - is to be considered immoral. This chapter will focus on the latter claims, which can be categorized into several clusters of arguments: (a) arguments that focus on the so-called integrity of the genome, the organism and the species; (b) arguments expressing the belief that animals have a good of their own; and (c) arguments questioning the technological interference with the natural order. We will demonstrate that the claim that it is ‘inherently wrong’ to tinker with the genetic make-up of animals, is not self-evident and even hard to maintain having investigated the underlying presumptions. Sound resistance to producing transgenic pigs is restricted to concerns regarding the concrete effects of the applications.

5.1 Introduction

Transgenic technology (transgenesis) involves the deliberate transfer of external DNA that renders the recipient a new, foreign property. The major utility of the technology lies in the possibility to allow for the desired expression of otherwise species-specific genes and traits in different species and for the subsequent transfer to the host's offspring. The initial method, which was first shown to be effective in 1980¹, consisted in introducing foreign DNA obtained with recombinant techniques into a newly fertilized mammalian egg. The DNA was shown to integrate into and proliferate with the recipient's native genome and eventually contributed to all cells of the developing animal (including gametes). The production of transgenic animals has become widespread since the development of the first transgenic mouse in 1981. In agriculture, animals are commonly manipulated to produce quantitative and qualitative changes in animal products that cannot emerge by conventional selection, for instance a larger production of milk, or the production of milk with enhanced qualitative properties (such as reduced lactose or cholesterol and increased concentrations of protein)². If the animals are made to consist of particular human genes, they may develop into preferred models for human disease or even provide human protein-generated medicines. Transgenesis of human genes into the genome of pigs has also allowed for the production of porcine grafts that are specially adapted to serve as potential replacement grafts for transplantation in humans. The prospect of using porcine grafts to meet the shortage of human cells, tissues and organs for transplantation is still remote due to problems related to immunology, the potential transfer of zoonosis and features involving the physiological interaction between the xenograft organ and the host. Nevertheless, the transgenic intervention of source animals to express human complement inhibitors such as DAH and hCD59 has proven to be effective to counter the first stages of hyperacute rejection and to reduce the risk of complement activation³. It thereby constitutes one of the major advances in xenotransplantation research.

Although the production of what some call 'humanized' pigs is based on an urgent human need for transplantable organs, the production of transgenic animals raises distinct moral questions^{4,5}. Various surveys have established that, although approval of transgenic manipulation of animals increases when carried out for the sake of medical progress, the general public adheres to strongly held moral objections to the genetic engineering of animals. Indeed, one public opinion poll reports a higher level of resistance towards the genetic engineering of animals than of humans, at least within the context of the genetic

engineering of food animals⁶. The aversion towards the production of transgenic animals can be seen as an echo of the public mistrust that has occurred ever since recombinant DNA research emerged in the early 1970's. That development implied a breaking point in history as it gave man the capacity to redesign living beings across the intuitively felt most stringent species boundaries. As John Harris phrased it:

We are now able to transcend the limitations of particular species and combine the virtues (and vices) of different species and indeed programme into species new attributes never before a feature of any species. We can, or eventually will be able to, create new 'transgenic' creatures of unprecedented nature and qualities.⁷

As is often the case with ethically charged issues, the creation of transgenic source animals is brought up for discussion with a jumble of both consequentialist and inherent-concern arguments. The consequentialist arguments against transgenesis point to the potential effects of the transgenesis, while the inherent-concern arguments question the acceptability of the principle itself. It is the latter kind of argument we are interested in here. The inherent-concern arguments claim that the manipulation of the genetic material is fundamentally wrong for its own sake - i.e. that the mere action itself, regardless of the effects, should be considered immoral. If that is the case, then the discussion needs not be taken further. If not, the arguments do not stand in evaluating the procedure. The focus should then be shifted towards other, consequentialist arguments in an attempt to establish whether there are genuine reasons to refrain from producing humanized pigs. It is from that perspective that it is worthwhile to examine arguments claiming that it is 'inherently' wrong to tinker with the genetic make-up of pigs (or that of any other animals).

5.2 Wrong for the sake of it

Although genetic manipulation has from the outset been promising, its appeal has not been widespread. To this day, the public perception is still largely that genetic engineering is 'morally wrong'^{8,9} and several surveys have established that particularly inherent concerns - as opposed to concerns regarding the effects - are the prevalent moral criteria in biotechnology debates^{10,11,12,13}. Based on a study of the literature on the ethics of genetically manipulating animals, and on an inquiry of both written and oral objections from several animal welfare organizations (Belgium, UK, USA) against the production of

transgenic pigs for xenotransplantation specifically, we believe that the major ‘inherent’ moral objections can be categorized into three clusters of arguments.

A first set of arguments could be called ‘Integrity Arguments’. They are all based on the idea that the genome, the individual organism, or the species should remain intact as a whole. A second category implies the ‘Intrinsic Value Arguments’: arguments that animals have a value of their own, independent of their relation or utility to humans. A third cluster is made up of the ‘Sanctity of Nature Arguments’: arguments questioning the technological interference with the so-called natural order.

We will demonstrate that none of the arguments pertaining to any of those broader clusters is valid as such and that the production of transgenic pigs for xenotransplantation is not ‘inherently’ wrong. That will lead to the conclusion that valid resistance to transgenesis is restricted to concerns regarding the concrete effects of the applications.

5.2.1 Integrity arguments

The ‘integrity arguments’ referred to here are based on the idea that transgenesis goes against the moral status attributed to the ‘wholeness’ of an organism, its genome or the species to which it belongs¹⁴. The concept of integrity, as vague as it is, implies that the state of being in any one of those levels is complete, undivided, or unimpaired. Authors who defend integrity arguments refer to a harmonious - quasi sacrosanct - unity that merits a respectful attitude irreconcilable with transgenic interventions¹⁵.

A first subgroup of adherents of the concept feels that transgenesis fails to respect the genetic integrity of animals. By adding genetic material from other sources, transgenesis alters genetic host sequences and is said to thereby undermine the interrelated parts of the unique genetic ‘whole’. The proponents assert that, by introducing foreign DNA into an animal’s genome, the integrity is violated “at its most fundamental level”¹⁶. Of all the arguments at issue here, this is perhaps the least convincing one. To start with, it is highly unlikely that the transgenesis required for xenotransplantation purposes is a threat to genetic integrity as it consists in the relatively precise transfer of only one or two genes. That aside, one could rightfully question whether there is such a thing as ‘genetic integrity’ at all, whether it can possess a moral status and whether violating the genetic integrity - no matter how it is defined - is specific to the procedures of transgenesis.

Advocates of ‘genetic integrity arguments’ seem to presume that it is the genetic make-up that is responsible for the unique traits of an individual animal. The ‘unique’ identity of an organism is naturally very hard to establish through reference to its genome alone. Of course, monozygotic twins (and clones, for that matter) illustrate perfectly the fact that the so-called ‘nature’ of an individual organism is the result of the interplay between genes and environmental factors. Furthermore, if anything, the genome of any one organism can hardly be unambiguously characterised by uniqueness, given that the most distantly related organisms share the majority of the genes. From that perspective, even the insertion of much more human genes in the genome of pigs is relative. Even if the concept of genetic integrity was more compelling, alterations in the genetic make-up of an organism are not specific to transgenesis. In general, the genome is not an unchanging, all-determinant essence, but the unplanned result of evolution. At a more individual level, the genome is constantly subject to change and division through, for instance, spontaneous DNA mutations and viruses. It is also far from clear why genetic integrity merits moral acknowledgement. Several opponents to that idea suggest that it is a fallacy to derive moral status from the biology of organisms rather than from their psychology. Savulescu, for instance, believes that the distinction between humans and chimpanzees should be drawn from the psychological differences - in the ability to reason, to act on the basis of normative reasons, to believe, among others - rather than from the mere 1.5 per cent of DNA that we do not share with each other¹⁷.

The fact that all species share a genetic basis also pinpoints some of the flaws in defending integrity on a species level. ‘Species integrity’ is used to refer to the unity of characteristics, qualities and dispositions that are specific to a species. Those traits are said to be shared by all members of the same species, by domesticated as well as wild animals. The arguments usually assert that it is wrong to interfere with the seemingly fixed boundaries that distinguish the different unique sets of species traits, which have been developed over hundreds of thousands of years and constitute an ecological harmony. A pig is a pig, and not a partly human pig.

This type of argument, too, has become less prevalent, perhaps because it has become more and more clear that there is no one way to delineate what a species is, let alone to define its particular integrity. At present, the biological literature consists of up to 22 different interpretations of what constitutes a ‘species’, thereby undermining the existence of a universally compelling concept¹⁸. Each of the taxonomies outline very

different defining characteristics, due to the lack of an unchanging set of species traits from which one can draw fixed species identities and boundaries^{19,20,21,22,23}. We owe that anti-essentialist insight to Charles Darwin, who demonstrated that the process of variation and selection is the drive of the continuous variety in nature. The evolutionary theory does not explain for any biological integrity, to the contrary. Indeed, Charles Darwin found evidence for the theory, and in particular for the theory of evolution by natural selection, in the preliminary changes in animal traits engineered by breeders and farmers through artificial selection among naturally occurring variants²⁴. A species is a categorical and, therefore, abstract word, and any reference to its 'integrity' is based on the qualities and characteristics of the individual members that are thought to somehow relate to each other. Even if we were to support - for the sake of argument - the perhaps most prevalent and paradigmatic definition of a 'species' - the biological species concept - which delineates a species as a reproductively isolated group whose members can interbreed and produce fertile offspring, transgenesis is unlikely to threaten that unity. Although at a genetic level the DNA of two species are combined, the production of transgenic pigs is still very far from creating crossbreeds. A microorganism with recombinant DNA usually still shows major similarities with its predecessors. And while we have created many radically new variants of crossbreeds ('tiglons', 'beefalos', etc.), we have never created a 'new' species that is reproductive and at the same time reproductively detached from the related animals.

Those who support integrity on the level of the individual organism argue that its 'fullness of being' must be respected, referring to the 'wholeness' and 'completeness' of the animal, including behaviour that is constitutive of the capabilities characteristic of the animal's 'nature'. According to one interpretation, integrity implies:

(...) the wholeness and completeness of the animal and the species-specific balance of the creature, as well as the animal's capacity to maintain itself independent in an environment suitable to the species.²⁵

Although the word has a nice ring to it, the notion of integrity is extremely abstract and it remains difficult to fully grasp its meaning, should it actually have one. It becomes devoid of any meaning when applied in cases where the animal itself is not even aware of the changes to its 'wholeness and completeness'. The most widely used technique of transgenesis, pronuclear microinjection, consists of injecting the human DNA into the genetic material of a newly fertilized egg²⁶. In another technique, the procedure is conducted even before the fertilization, the human DNA being inserted in the swine sperm,

which will later be used for fertilization²⁷. As one author puts it: how can we speak of the integrity of an animal at the moment that it does not yet exist?²⁸ Furthermore, while an organism's defining characteristics can be affected by concrete changes in the habitat of the individual animal or by obvious physical handicaps, there is no reason why a transgenic pig should differ substantially from one that has not been subject to genetic manipulation, granted that the procedure was a success. Although we do not believe in such an essence, if we grant - again for the sake of the argument - that there is such a thing as 'the pigness' of the pig, the pig does not seem to lose any of its 'pigness' through the insertion of one or more human genes meant to counter immunological rejection.

5.2.2 Intrinsic value arguments

There are different interpretations of the notion of intrinsic value and different reasons for attributing it. Generally, the concept stands for the conviction that animals have a value of their own²⁹ and that that value is independent of other things, persons or interests³⁰. In this sense, the intrinsic value of an animal exceeds the utility value it has for humans, a notion that finds growing support in our society. The strength of the argument results from the intensification of the way animals are being used and reduced to instruments of technology. Although the instrumental - and thus anthropocentric - approach towards animals is not exclusively associated with biotechnology, it is said to be enhanced by recent trends of genetic manipulation and by the reduction of 'living wholes' to DNA. More importantly, perhaps, the transgenesis is not applied to alleviate or prevent a genomic defect in the animal, but rather to optimize its biology for human utility³¹.

Several authors emphasize that only by acknowledging that animals are of value for their own sake, they become an object of true moral concern. The concept of intrinsic value - sometimes considered a sacred quality³² - is thus meant to extend the moral domain from humans to other entities, animals and, in some interpretations, even plants or the whole of nature. While we acknowledge the importance of extending the domain of moral concern to include animals, we believe that reference to an intrinsic value is a weak and unconvincing foundation of such reasoning and is, in any case, irrelevant within this context of genetic manipulation.

The argument that animals have intrinsic value is most often derived from the Kantian maxim, which summons us never to treat others as a means only, but as 'ends' in

themselves. In extending respect for one's 'ends' to animals, most authors refer to the concept of '*telos*', a concept that verges on the notion of integrity. Aristotle defined *telos* as the full flourishing stage of a creature's existence and used it as a tool to derive and explain the nature and existence of its chief functional and physical characteristics³³. In talk of the intrinsic value and goodness of an animal, *telos* is used to refer to the set of traits that constitute the specific nature and needs that are characteristic of an animal (including physical constitution, behavioural and psychosocial repertoire). The conservation of normal development and expression of *telos* is granted an absolute value³⁴.

It is nevertheless well contested whether there can in fact be an absolute value inherent to animals. Generally, intrinsic-argument objections arise in response to situations that cause the animal to alienate from a given set of functional needs and that result in frustrations of the animal in the inability to fully fulfil its *telos*. Those arguments thus relate to the potential effects of transgenesis, rather than to the principle itself. Furthermore, the argument can be made that the intrinsic value related to an animal's *telos* is highly conditional rather than absolute. Indeed, the value is made dependent of the extent to which the animal is aware of the suffering that relates to the inability to satisfy its nature. Those prevailing interpretations are extensions of an anthropocentric viewpoint as they pertain to sentient ('higher') animals only and constitute what Henk Verhoog calls the 'zoocentric approach'³⁵. Even for sentient animals, reference to the moral value of their specific natural *telos* does not constitute sufficient reason to sustain it. Indeed, the compromise position taken by Bernard Rollin rests on the argument that:

One cannot argue that because it is wrong to violate the various aspects of a certain animal's *telos*, given the *telos*, it is therefore wrong to change the *telos*.³⁶

While Rollin objects to violations of the nature-specific interests of an animal, given the frustration that would cause to its *telos*, he advocates the introduction of entirely novel sets of functional needs and interests, or at least the removal of those interests that would cause suffering. He illustrates his point with the example of battery farm chickens: if one could eliminate their nesting urge, that would not be wrong, as the chickens would no longer suffer from being caged³⁷. Against that viewpoint, Verhoog defends a 'biocentric approach' in which all living beings are said to have a good of their own that is the product of evolutionary history and that merits respect regardless of sentient suffering³⁸. For Alan Holland, too, the notion of intrinsic value of a being's *telos* is absolute. Even beneficent changes to an animal's *telos* "puts respect for the states of a subject above respect for the

subject” and would not avoid the criticism that “one was using an animal’s nature as a means, and failing to respect its ends in the process.”³⁹

A well-known counter-argument to the concept of intrinsic value is the claim that animals cannot have a value independent of humans⁴⁰. In other words, the intrinsic value of animals is not an objective one, but rather a (subjectively) *attributed* one. As the capacity to attribute value is specific to humans, it is a fallacy to say that animals or any other natural entities can have an absolute and objective value of their own. The value itself does not exist ‘out there’. That is not necessarily a reason to reject the validity of the concept. Indeed, van den Bos concludes that, as the intrinsic value of an animal is not based on any objective referent aside of the human referent, it is the responsibility of humans in their relationship with animals to properly include them in the moral domain⁴¹. That is again a very anthropocentric view, which the author admits, but it allows for a respectful attitude towards animals that is proportionate to the respect due to humanity. According to those authors, the moral worth of animals is not necessarily absolute. There may be compelling reasons to allow infringements on the intrinsic value with regard to the moral concern due to humans⁴². In that sense, one could argue that the potential to save lives through xenotransplantation would to some degree justify infringements on the intrinsic value of the source animals.

What is left, then, of the so-called ‘intrinsic value’? If a value is intrinsic, then by definition it belongs to the thing itself, and is acknowledged and recognized, rather than attributed. What is the meaning of an intrinsic value when it is dependent on the goodwill of people, and of the negotiation that is constantly made between this value and other (man-related), potentially more stringent values? The concept is not only contradictory and hollow, it is also superfluous: we do not need the notion of ‘intrinsic value’ to take up moral responsibility towards animals (nor towards humans, for that matter). It suffices that we acknowledge their interests, of which an interest in freedom of pain and stress is the most elemental, and which are in fact matters of consequences rather than inherent concerns (we will explore that issue in further detail in the next chapter). Furthermore, even if there were such a thing as intrinsic (animal) value, then it would still be absurd to say that it could be threatened by the manipulation of genes. That would be like saying that a person with an artificial leg or dentures has lost some of his or her intrinsic value.

5.2.3 Sanctity of nature arguments

The key notion in all ‘sanctity of nature arguments’ is that genetic engineering is immoral in so far as it blurs species boundaries, meddles with nature, violates the sanctity of life, intervenes with a natural order and stimulates human’s inappropriate pretension to omnipotence. Rollin puts the underlying presumption as follows:

There are certain things man was not meant to do (...), and genetic engineering of animals is one of them.⁴³

With regard to our discussion here, two commonly held convictions can be distinguished: the production of transgenic animals is a violation of either divine creation or of the natural order. From both perspectives, the idea arises that he who elevates himself to manipulating processes of life, goes too far. Those are the well-known ‘playing God’-arguments, and the dangers of the illusion of man almighty have been cited since antiquity.

The first type of argumentation is based on the belief that the transgenesis goes against the will of God, granted the belief that he created living things, each according to its own kind. That claim is not self-evident as there is, of course, no objective reason why one should prefer such interpretation to the non-normative scientific conception of nature. Again, we owe to Darwin the insight that no living being has been specifically created; that the variation of fauna and flora is the result of a continuous and unplanned selection mechanism allowing new and beneficial traits to be passed on.

The second type of argumentation, just as ‘mystical’ in character as the previous one, pertains to the presumption that nature is unique and sacred and should not be altered. Transgenesis is then seen as a violation of the natural order and of the natural spontaneous development. However, the assertion that what does not lie in the course of nature is wrong by definition, is based on invalid rhetoric.

For one, the claim that something is or is not ‘natural’ can be interpreted and valued in different ways according to the context and intent. Once again, we have to make do with a very ambiguous term. Let us say, for instance, that we define ‘natural’ in very general terms, as that which is the product of a development in nature, of the laws creating and controlling things in the universe. Following that description, the production of transgenic pigs is, in fact, a very ‘natural’ phenomenon as it is based on the application of nature’s

laws. In that sense, all that occurs, even in a laboratory, is a product of natural processes, explicable in terms of natural science. Furthermore, transgenesis does not contravene the spontaneous development of nature since it can occur in nature without the intervention of man. Indeed, in an alternative method to obtain transgenesis, retroviruses are used as ‘vectors’ for transferring foreign DNA into sperm precursors and oocytes, building upon their natural ability to become integrated into the genome of different hosts. Following a different interpretation of ‘natural’, however, one might stipulate that transgressing species boundaries may be a very natural thing for retroviruses to do, while it is not natural for humans to do so⁴⁴. But what we are asserting then is that the wrongness lies in the interference of man into nature and that ‘nature’ should be more specifically defined as the process unrelated to human intent. Such a view relates to the fundamental conception of nature as distinguished from the domain of culture. If that is so, then, as has long been argued, one should level this objection to traditional breeding methods, which also cause alterations to the animal’s genome through a specific human intent and intervention. Moreover, such a concept gravely limits what is often intuitively regarded as nature. Even forestry is a clear example of how man interferes with nature. As a matter of fact, it is extremely difficult to think of examples of what is referred to as purely ‘natural’ in this sense, as human interference has intertwined with nature at very many levels in the advancement of civilization.

Secondly, further motivation is required for maintaining that the natural genomic make-up of an animal is of greater value than that which has undergone genetic manipulation. It is an odd step to attribute moral status to natural development, a development that is not consciously aware of good or evil⁴⁵, that is simply not interested because it does not have the capacity to care, and is the result of the interplay between coincidence and selection, rather than of planned design. Claims that what is ‘natural’ is better than that which is ‘unnatural’ also preclude the fact that natural events are not automatically good and can have negative as well as positive effects. That is an insight we constantly endorse when we attempt to improve the natural state of ourselves and of our environment through curative and preventive medicine, agriculture, urbanization, etc. The underlying evaluation of our so called pretension to interfere with nature should not be based on whether or not we have the right to do so, but whether the action will attain worthy goals.

5.3 Concluding remarks

During the past decade, public awareness of the moral status of animals has increased and has caused extensive debate on matters of genetic manipulation. With regard to the production of transgenic pigs for xenotransplantation purposes, it is, however, in no way evident that that application is in itself immoral. Accordingly, we should not allow such arguments to stop or hinder the development of something that is of potential benefit to humans. It is, indeed, still uncertain whether either this or any other technique will ever allow a future of unlimited, safe and effective xenotransplantation for humans with organ failure. Nevertheless, it should be clear that the type of reasoning we have focused on here should not stand in the way of exploring that potential.

Although we reject the inherent arguments, we are not saying that the production of transgenic pigs for xenotransplantation purposes is entirely unproblematic. The concrete consequences of the procedure are of interest in their own right. In the shift to consequentialist arguments, perhaps the specific context of breeding transgenic pigs for xenotransplantation purposes would dismantle an exaggerated and unnecessary emphasis on various potentially bad outcomes in comparison with other applications of transgenesis. For instance, discussions on the use of transgenesis often reveal the concern that the application will have baleful environmental impacts^{46,47,48}. The prospect of loss of genetic diversity and of causing ecological imbalance, however relevant for some applications of transgenesis, is of little concern here as the genetic alterations are negligible. Moreover, it could still be argued that, as new genes are inserted rather than removed, transgenesis may be thought of as a potential for increasing rather than threatening genetic variation⁴⁹. The experiments under discussion here are also less invasive than experiments that induce deliberate changes to central animal functions and that can reasonably be expected to have resultant effects upon animal welfare. In an early experiment to enhance food animals, for instance, researchers inserted the gene for human growth hormone into pig embryos and found that the resulting animals suffered a painful arthritic condition so severe that the experiment was discontinued and the pigs euthanized⁵⁰.

Nevertheless, there is plausibly more to say for the idea that producing transgenic ‘source animals’ can have harmful effects on the pigs themselves, even if no changes in phenotype are intended. In general, transgenic procedures have a bad reputation in that they have been subject to trial and error, yielding imperfect and fairly unpredictable expression of transgenes. Due to the poorly controlled integration of DNA, the possibility exists that a

transgene will insert in an unintended physiologically important region of the genome, leading to unexpected harmful physiological effects. It is also possible that transgene insertion could inactivate a tumour-suppressor gene or lead to unrelated, harmful mutations of the foreign DNA in the host's genome⁵¹. However, such outcomes have only rarely been observed⁵². More common is the event that the transgenes are not, or insufficiently, expressed. Of the animals developed through pronuclear microinjection, only 10 to 40 per cent test positive for transgene genetic sequences⁵³. This necessitates the killing of the majority of the non-transgenic offspring that fails to become transgenic. Further killing occurs when, depending on the degree of precision of genetic manipulation required, the transgenic offspring do not satisfy desired criteria of transgene expression⁵⁴. In our setting also, the sow may suffer from the particular procedures involved in pronuclear microinjection, including the retrieval of embryos for genetic manipulation and the subsequent reinsertion in the womb⁵⁵. Sperm-mediated transgenesis allows for the transgenesis to occur upon fertilization and, if coupled with artificial insemination, proves to be non-invasive in comparison, but has not been established as an equally viable method.

The question that the potential consequences of transgenesis raise is whether the harm done to the animals can be justified in light of the prospective benefits that may arise from the procedure. Adverse effects on animal welfare are however not only related to unsuccessful or intrusive transgenesis, but are most typically observed as a consequence of the surgical procedures subsequent to transgenesis, inappropriate accommodation and laboratory conditions as well as the specific purposes for which the animals are bred^{56,57}. Granted that the killing and suffering of porcine source animals is an inevitable element of the purpose for which they are bred - to provide specified-pathogen-free transplantable grafts - a discussion on the justification thereof will be the subject of the next chapter.

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6 Use of pigs for xenotransplantation: the speciesism by proxy syndrome.

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Abstract

One of the most pertinent ethical issues related to xenotransplantation is the question whether the use of animals as sources of cells, tissues and organs for animal-to-human transplantation, is acceptable. Justifications of that practice often shift focus from this question to the question whether it is more ethical to use one type of animal (the pig) rather than another (the nonhuman primate). This chapter examines the tenuousness of three ethical arguments commonly rehearsed in defence of choosing the pig as source animal: (a) that the use of pigs for human purposes is embedded in a long tradition; (b) that pigs are not an endangered species; and (c) that they do not share the cognitive and emotional capacities with humans to the same extent that primates do. On first thoughts, those arguments seem translucent and the debate intelligible. However, this chapter will show that those arguments fail to demonstrate that it is in fact acceptable to use pigs as xenograft sources. The lack of clear morally relevant distinctions between pigs and primates will be the main point of criticism towards common justifications of using pigs as source animals. Further justifications will be evaluated in light of contesting views and modern animal welfare theories.

The Pig, if I am not mistaken,
Supplies us sausage, ham, and Bacon.
Let others say his heart is big,
I think it stupid of the Pig.¹

6.1 Introduction: from primate to pig

One of the most obvious issues in discussing the ethics of xenotransplantation is the question if we may breed and kill animals on a large scale to serve as sources of transplantable cells, tissues and organs for humans. In recent debates on xenotransplantation, interest in animal welfare issues associated with the production of pigs as sources of xenografts seems to have faded somewhat. Many experts will agree that the question if use of animals is morally acceptable has made way for questions if the technique will ever be safe for humans. Moreover, it seems as though the question if it is acceptable to use animals as sources of grafts is replaced by the question if it is more ethical to use one type of animal (the pig) rather than another (the nonhuman primate).

As noted in the fourth chapter, ever since the early 17th century, clinical xenotransplantation has been attempted using all types of animals (including sheep, rabbits and frogs). For most of the early trials in the 20th century, however, the animal of choice was the baboon or chimpanzee. The use of these (higher) nonhuman primates was thought to best warrant graft survival because of their genetic and anatomic similarity with humans. Today, the confined breeding of large populations of chimpanzees or baboons for ‘spare parts’ is troublesome² and has been condemned by various regulatory authorities^{3,4,5}. The reluctance towards using nonhuman primates is rooted in serious practical problems, which include incompatibilities in organ size, their slow breeding potential and a higher risk of cross-species virus transfer. There are also sufficient and convincing ethical reasons that stand in the way of using nonhuman primates as sources of xenografts. Well-cited are concerns based on their humanlike traits, their relatively scarce use for human purposes and their potential for extinction^{6,7}.

It is often argued that these objections are by-passed when considering the use of pigs as source animals. The pig:

(...) although domesticated and familiar, is too distant to evoke the same feelings we have for primates, has the correct-size organs, is probably less likely to pass on infections, breeds rapidly, and is not endangered; moreover, millions of them are eaten every year.⁸

Justifications to use pigs thereby elicit much less opposition and find wide regulatory support. I find this ‘comparative method’ - which is commonly applied in the literature - a weak foundation for dismissing opposition towards xenotransplantation from an animal welfare point of view. Even for convinced advocates, it may be worthwhile to examine some of the weaknesses that shelter within each of the following arguments: (a) that the use of pigs for human purposes is embedded in a long tradition; (b) that pigs are not an endangered species; and (c) that they do not share the cognitive and emotional capacities with humans to the same extent that primates do.

Those who feel that the rearing of pigs as xenograft sources is wrong generally refer to the unacceptability of exploiting and killing pigs to serve as resource utilities for humans. In addition, objections are raised towards the specific circumstances under which the pigs are born, raised, and killed - circumstances which are said to compromise animal welfare and elicit significant suffering^{9,10}. It must be noted that welfare issues are not as much of an issue in most cellular xenotransplantations, in which case the cells can in principle be obtained from pig fetuses. For those animals that are brought to life as sources of transplantable organs, by contrast, and as noted in the previous chapter, some degree of physical suffering may result from unsuccessful transgenesis procedures. Arguably, this is the only type of *physical* suffering that cannot be excluded, granted that high and exemplary standards for the housing and care of the animals are complied with. Indeed, some xenotransplantation guidelines provide detailed instructions to take proper care in achieving an appropriate atmosphere and temperature, a healthy diet, environmental enrichment, and other biological needs of animals¹¹. Conceivably, if these standards are met, the remaining suffering at issue is of a ‘*psychological*’ rather than of a directly ‘*physical*’ nature. Psychological distress may in particular result from the high health status required to optimize the safety and quality of the animal grafts prior to clinical use. Most importantly, to reduce the risk of xenozoonosis after transplantation of porcine grafts, stringent measures are taken to prevent contamination of certain bacteria and virus in the source animals¹². With this intent, the pigs are often brought forth by way of hysterotomy and the sow is killed once the piglets are retrieved. The young are foster fed by gloved human hands and reared in barrier facilities free of identified pathogens (Qualified Pathogen Free conditions). The conditions under which they are reared are comparable to those of laboratory animals with restrained space allowances. These

facilities are barren, sterile environments that potentially subject the pigs to sensory deprivation and deny the manifestation of natural behaviour like rooting and foraging¹³. The pigs are subjected to extensive and routine infection tests and confined to living in small groups. This may deprive them of sufficient social interaction, particularly the weeks before the harvest of the xenografts, during which the animals must be quarantined. Additional stress is conceivable due to transportation prior to the killing, which might be necessary if the distance to the transplantation site would compromise the quality of the xenograft. In light of these concerns, a justification of organ xenotransplantation must be carefully considered.

6.2 The prize animal

Despite the fact that baboon and chimpanzee organs are both anatomically and physiologically similar to human organs and - in comparison to non-primate xenografts - have a smaller chance of being instantly rejected by the human recipient's immune system, two practical arguments support preference for the use of porcine organs. First, baboon and chimpanzee organs are too small and appear to be suitable for paediatric transplant recipients only. Second, the genetic relationship between nonhuman primates and humans is so close that it increases the risk of virus transmission.

As for the problems related to organ size, it is especially the size of primate *hearts* that is of concern. The problem should be less obvious regarding the use of kidneys, for which size is not so relevant, and the liver, which is to a large extent capable of regenerating¹⁴. Nonetheless, herds of miniature swine have been bred that have a body weight similar to human adults and provide us with all organs of adequate size¹⁵. However, given that there is much more to effective transplantation than merely matching organ size, this is as far as the direct physical advantages of using pigs extend. As reviewed in the fourth chapter, severe immunological and physiological obstacles form an enormous obstacle to effective transplantation of organs from this discordant species^{16,17}. Furthermore, while the species barrier between nonhuman primates and humans is particularly easy for viruses to cross, history has in fact taught us that close contact with pigs is not without risks either. We currently know of various viruses in pigs, which have elicited serious morbidity and mortality when transmitted to humans¹⁸. Particularly illustrative in this respect is the 1918 influenza virus, which killed up to 50 million people¹⁹. The 1998 outbreak of the pig-derived Nipah virus in Malaysia unforeseeably caused systemic infections in humans and

killed more than half of the 200 people infected²⁰. Containment of the source animals in specified pathogen free environments and highly sensitive assays could eliminate these and other identified exogenous viruses. Recent advances in research have also diminished fears with regard to the replicant and recombination competence of several known porcine endogenous retroviruses^{21,22,23}. Nonetheless, such measures cannot exclude the possibility that there are other, unknown and undetectable viruses that could be harmful in a human host. Those uncertainties make way for a varying taxation of the virus risk and do not render the validity of using pigs for safety reasons self-evident.

Perhaps the most obvious practical consideration is the fact that pigs, in contrast to primates, are relatively easy to breed, to genetically manipulate and to develop industrially. The use of higher primates as source animals would not resolve the current organ shortage, for it would be practically impossible to derive a sufficient amount of organs. The breeding of primates is difficult and time-consuming²⁴, with a very low reproduction rate (one offspring per gestation). Pigs, by contrast, have a good breeding potential (between 5 to 12 piglets per litter) and rapid growth to reproductive maturity. The fact that maintenance of a pig breed is much less costly than of baboons adds relevancy to that argument as well. Apart from those considerations, it is not directly clear that pigs should be used for practical reasons. Similarly, the persuasiveness of commonly held moral arguments supportive of a preference for pigs remain contestable.

One common moral reason to justify the use of pigs over primates rests on the fact that we have a long tradition of slaughtering pigs for human purposes. While nonhuman primates are, at least in western culture, not killed for food, pork has provided nutrition for thousands of years and currently constitutes the greatest proportion of the world's meat consumption (with 98.1 million pigs killed in 2000 in the US alone²⁵). Even in medicine, the pig is used for its heart valves and skin grafts and for the production of other porcine-based pharmaceuticals²⁶. Hence, the rationale is that, given the longstanding tradition, it would be inconsistent to deny use of pigs for that additional purpose²⁷. While it is probable that the general public sees little or no moral distinction between killing pigs for food or for medicine²⁸, that reasoning is a tenuous justification from several points of view.

For one, it could be argued that to determine if an action is right or wrong, it should not have to depend on whether or not it is embedded in tradition. Tradition and custom might be the standard for intuition; however, they should not serve as the ultimate point of reference for ethics. Put simply, otherwise we could not ethically condemn practices that

were longstanding but are - for good reasons - no longer tolerated, such as slavery and child labour. It would be misleading to conclude that xenotransplantation is ethical, given the tradition of pig slaughtering is not in itself indisputably ethical. To those who believe that the killing of pigs for human ends is problematic, a deeper motivation is in place. It may for instance be argued that, whereas the killing of pigs for food is unethical, the killing of pigs for medicine is valuable, since use is made of one life to save others. Two, there may be a point after which it is felt that xenotransplantation is not merely part of the tradition of killing pigs, but actually exceeds standard practice by introducing a significant increase of the amount of animals killed and a new way of consuming animals. That concern may be heightened by fears that the animals will be inefficiently used, for instance, if one pig is to be killed for only one organ transplant. Conceivably, one could argue that the slow progress obtained in survival rates of pre-clinical animal xenotransplantation research has already involved a significant waste of animal resources. Three, perhaps the *killing* of the animals is not the focus of moral concern, in that it may be argued that the killing in itself does not necessarily elicit suffering. Such reasoning could lead us to reserve our moral concern for the suffering during upbringing. Proponents of such a view may defend the killing of a source animal in comparison with the gruesome alternative of subsequently harvesting its organs, tissues and cells. Focus on the quality of life could also lead one to argue for the use of pigs as sources of xenografts rather than as sources of consumable meat products, given the cruel conditions of most pig meat industries. However much you argue for or against the case, an ethical evaluation of sacrificing pigs for xenotransplantation is not derivable from reference to the longstanding tradition of slaughtering pigs.

A second commonly maintained moral argument holds that large-scale use of chimpanzees and baboons for xenotransplantation is unethical, as it would imply a significant pressure on their species-survival²⁹. Accordingly, due to the fact that the 'pig species' is not endangered, the use of pigs as xenograft sources *is* ethical. Following that train of thought, however, if chimpanzees or baboons were not (potentially) endangered, the ethical judgment should be different. Indeed, Donnelly, for instance, points out that it could be morally legitimate to use chimpanzees in xenotransplantation research if it did not threaten the species³⁰. That implies that the good of the species outweighs that of the individual. Subordinating the individual to the group is a debatable defence of animal welfare and has, in our opinion, been persuasively countered by Bernard Rollin in noting that:

As far as we are concerned, it may be far worse to kill the last ten Siberian tigers than ten other Siberian tigers when there are many of them. (...) But as far as the tigers are concerned, they don't know or care whether they are the last, and thus it is equally wrong from a tiger's perspective (if it is wrong) to kill any ten or the last ten.³¹

While it remains questionable if an individual tiger *can* conceptualize or care about its own death, it is evident that a 'species' - be it that of a tiger or of a pig - cannot. The term 'species' is an abstract collective noun and does not refer to a sentient being. If the 'pig species' were to become extinct, that could only be of concern to pigs in the form of their individual and concrete suffering. Likewise, pigs used as a xenograft source are not solaced by the thought that, although they may suffer and die, The Pig will never cease to exist.

A last and undoubtedly most complicated argument we would like to discuss here holds that exploitation of pigs is *less* problematic than exploitation of primates as pigs do not share cognitive and emotional capacities with humans to the extent that primates do. That argument can be interpreted in at least two ways. Either it implies that pigs are too distant from humans and, as such, are not part of their 'moral community', whereas primates are. Or it implies that pigs do not have the capacity to suffer from the physical or psychological consequences of being bred for organs to the extent that primates do. Neither of these interpretations warrants that the exploitation of pigs is *unproblematic*.

As for the first interpretation, a lot of unease towards using primates for research stems from their 'kinship' to humans. They seem too closely related to us, and their behaviour too similar to ours, to feel that they are not due some of the moral concern we would express towards other humans. Especially the Great Apes share many characteristics in terms of mental and emotional capabilities, characteristics which most of us would include in describing what it means to be human. Pigs, by contrast, do not appear to share many of those characteristics and show much more profound differences with humans.

While that may be the case, it has been well-argued that:

(...) the issue is not whether they are different, but whether they are different in morally relevant respects.³²

Unless the moral relevancy of having or lacking such characteristics is demonstrated, differential treatment on the basis of kinship is a vulnerable target of 'speciesism' critics. Speciesism is said to be comparable to racism and sexism in that it contains a prejudice against members of another group (another species) in favour of the own group. While

there is a noteworthy volume of literature that embraces speciesism³³, many authors have shown that it is inconsistent and unattainable. A mere description of the characteristics generally possessed by a group - in this case, Great Apes and humans - will in itself not justify *morally* distinguishing between other groups. And according to Peter Singer:

(...) it is not difficult to see that there is no morally important feature which all human beings possess, and no nonhuman animals have.³⁴

Singer attacks the presumptions underlying the common belief that the interests of humans are superior to those of other animals. He argues that the grounds for giving animals unequal consideration must also apply for different human beings. The idea is illustrated by the 'argument from marginal cases': the argument that the characteristics that are said to make humans morally distinct from animals, are lacking in atypical humans such as infants or mentally handicapped. Consequently, we should grant both atypical humans and animals with similar interests the same consideration. Given the strongly held claim that all human beings are equal, it would seem better to uplift the moral concern for the interests of such animals rather than to downgrade the concern for atypical humans.

In our case, however, the argument is not speciesist towards primates. Here, a species is excluded from moral concern with reference to a species that we have not excluded. I call it a 'speciesism by proxy' in that the speciesism has merely been shoved further away. Granted that certain nonhuman primates do have some of the higher cognitive and emotional capacities pigs lack, it is not directly clear why this would merit different treatment. Following the marginal argument, for instance, one could find difficulty in defending the use of pigs over primates when little or no difference can be made between a very 'clever' pig and an utterly 'stupid' chimpanzee. The only reasonably relevant differences in emotional and mental capacities that would allow for us to subordinate the interests of pigs to those of humans and nonhuman primates would relate to indications that pigs cannot significantly experience the harm done to their interests. That is ultimately the subject of the second interpretation: the idea that pigs cannot suffer from the exploitation involved in xenotransplantation to the extent that primates can. Comparing the capacity to suffer between different animals and weighing its moral relevance is, however, an extremely complex issue and even more subject to debate.

6.3 Hogging moral status

Sykes *et al.* observe that according to some authors, whether or not an animal should be used as a source animal, should depend on whether the animal is sufficiently aware so as to be able to suffer from it³⁵. It is worth questioning whether a xenopig can suffer in such a degree that it can feel harmed by the specific conditions of its upbringing: the lack of a natural environment and the inability to express certain natural behaviours amongst the sow and siblings. In the words of Duncan:

Has a pig that's never seen a mud hole ever imagined one? Wanted one?
Needed one? Felt deprived when it didn't have one?³⁶

The problem we are confronted with here is extremely difficult as we are asked to find evidence for something that is ultimately a subjective experience, not accessible to outsiders. The peculiarity of such subjective experiences, however, is just as striking amongst humans as it is between humans and nonhuman animals³⁷. We seldom doubt that other humans actually do have subjective experiences and we generally gather our intuition from the resemblance between their behaviour (their expressions of pain, for instance) and our own, and from similarities in physiology and anatomy. Accordingly, analogies between humans and many animals in behaviour and homologies in the nervous system are increasingly depended on as a means of inferring information about their inner life³⁸. While we stretch the anatomical analogy between a pig and a human organ to the limit, it would be unreasonable to suggest that homologies in behaviour differ *completely* in relation to inner subjective states.

6.3.1 A clever pig extracts a deep root

The perception that humans have formed of pigs throughout the domestication of these animals may to a great extent preclude the observation of significant behavioural similarities between pigs and humans. Arran Stibbe points out that our presuppositions of pigs being “ignorant, greedy, untidy, stubborn, selfish, badly behaved and fat” once provided a necessary barrier between humans and pigs, “overcoming cultural taboos against killing those who are close to us”³⁹. Increasing knowledge of pig behaviour is starting to undermine that negative image. Given the right opportunities, even a layman will observe that pigs are in fact very clean and social animals, able to communicate with each other using a wide range of sounds. Pigs are prone to the so-called Porcine Stress

Syndrome and may show stressful, aggressive behaviour (tail-biting) in barren and overcrowded environments. Experimental tests demonstrate that pigs also have several complex inquisitive, problem-solving and anticipatory capacities which allow them to strategically interact with their environment. Research by Wood-Gush *et al.* demonstrates their motivation to explore novel stimuli independent of any primary reinforcement. In one study, it was found that piglets housed in barren environments spend more time investigating a novel area or a novel object than more fortunate animals⁴⁰. A second study demonstrated preference for an area with a new object over an area with a known object⁴¹. Experimental settings have also provided evidence that pigs are able to anticipate long-term consequences and act accordingly. In a preference test that provided different spaces, each relating to different periods of confinement, pigs quickly anticipated the duration of confinement in each setting and opted to enter those spaces that had short- or medium-term confinement⁴². According to Stanley Curtis, professor of animal sciences at Pennsylvania State University, pigs are in some respects as ‘clever’ as chimpanzees. Curtis has trained pigs to manipulate joysticks with their snouts and to ‘play videogames’ on a computer and believes that the animals thereby demonstrated important problem solving abilities⁴³.

At the very least, observations of subjective experiences in pigs are highly suggestive of a capacity to process experiences, which is much more complex than a direct reflex to pain or discomfort. The relevant question then - if we accept that those processing capacities are indicative of a capacity to suffer ‘psychologically’ - is whether that capacity is compelling enough for us to condemn their use as xenograft sources.

6.3.2 The moral relevance of suffering

Most reports and guidelines on the use of pigs in xenotransplantation demonstrate that that is not the case. For instance, in an influential report on ethical issues raised by xenotransplantation, the Nuffield Council on Bioethics emphasized the role of self-awareness as the guarantee that pigs do not suffer significantly:

Most significantly, for the purposes of this discussion, it has been argued that suffering and death are uniquely painful to a self-aware being who not only senses pain but can also perceive the damage being done to his or her self and future.⁴⁴

Self-awareness is held to be the prerequisite of any form of 'personhood', and is said to be dependent on:

(...) a high degree of intelligence, the capacity to make comparisons and judgments, and a language with which to articulate.

Here, again, a list of defining and distinguishing characteristics is given. But in contrast to a clearly speciesist approach, a reason is included as to why such characteristics must be taken into account. The idea is that self-awareness is the guarantee that there is a capacity to suffer significantly.

It is generally accepted that higher primates possess complicated cognitive processes, and several (less generally accepted) studies provide proof of self-awareness through mirror tests and even symbolic language usage in certain chimpanzees^{45,46}. Hence, a cautious and respectful position would judge that most of the higher anthropoids should not be subjected to such forms of distress, as it would cause significant suffering. Pigs seem to lack the important prerequisites for 'unique pain' and thus appear to be rightly excluded from equal moral concern. Nevertheless, the criteria used here rest on shaky grounds.

To begin with, identification of the relevancy of self-awareness with regard to suffering and pain should be consistent. As such, it is flawed to exclude use of certain primates as source animals but to tolerate continued and large-scale use of baboons and certain monkeys for xenotransplantation vivisectionist research purposes. That practice demonstrably elicits much more suffering than being bred as source animal. Indeed, a detailed investigation of a British xenotransplantation research facility (under the direction of Imutran) - submitted to the British Home Office - reported a great deal of suffering that was the result of post-xenotransplant rejection and infection⁴⁷. Second, the Nuffield Council interpretation of unique suffering is debatable. Focus on the higher cognitive prerequisites of self-awareness could lead us to exclude Alzheimer patients from the relevant moral concern, and we do not believe that that lies in their intention. Furthermore, and notwithstanding the broad philosophical tradition in which consciousness is based on language, there is growing conviction that self-awareness is not the direct effect of an innate capacity to form words and sentences. Damasio, for one, gives a convincing account of why the basis of self-awareness must be nonverbal, in that the starting point of language is always the translation of non-linguistic events, relations and concepts into words and sentences⁴⁸. Other authors stress the importance of nonverbal communication skills in many animals, including powerful olfactory perceptive

mechanisms⁴⁹. Alternative interpretations of self-awareness exist that do not necessarily require language or the other highly cognitive criteria. In fact, it could be argued that the word 'self-awareness' is a tautology: you cannot be aware without having a self. You cannot be aware of anything without knowing that it is *your* awareness. When a bee stings you, you will at the very least be aware of the fact that *you* have been stung. That elementary form of self-consciousness - 'sensation' - has nothing to do with any form of cognition. In this sense, the basis of self-consciousness is sentience; the capacity to experience episodes of positively or negatively valued awareness. Animal liberationist views will argue that it is in the interest of all sentient animals to seek positive experiences and avoid negative ones, no matter what the size or shape of the individual experiencing it. To the extent that both pigs and nonhuman primates share that interest, it deserves equal consideration.

The moral significance of sentient experience forms the major obstacle to justifying use of pigs for xenotransplantation purposes. Animal welfare objections are not directly bypassed in reference to a higher complexity of self-awareness. The Nuffield Council suggests that self-awareness implies an ability to anticipate the future to some degree, to regret that the confinement will stand in the way of further pleasure seeking. It is not per se clear that a pig's lack of such a level of awareness constitutes less of an assault on its immediate interests and why this would merit unequal consideration. In fact, the opposite may be the case: being kept in isolation and in a barren environment could arguably be a greater source of harm to the interest to seek pleasure and prevent suffering for a pig than for a human. A human, precisely because it has the ability to foresee and understand what will happen, how long the isolation will last and why it is enforced, may suffer less than the pig, whose awareness of frustration, anxiety or deficiency cannot be put in perspective in a similar way. The major strength of the referring to the concept of self-awareness, nonetheless, lies in the suggestion that a pig cannot be harmed as much *death* as humans can.

6.4 Life is what happens while you are busy making plans

The argument could be made that, whereas pigs have a capacity to suffer that should be taken into account, killing cannot harm them because they cannot *suffer* from their being killed. Granted that they are slaughtered humanely (painlessly, unexpected, and with no additional stresses), pigs are not aware of the fact that life is taken from them, and thus

cannot be thwarted in their interests. Conversely, critics may still deny that the harm is eliminated by eliminating the experience of harm done to one's interest. Indeed, otherwise one could suggest that the humane, unexpected and unconscious killing of humans does not constitute a harm either. The harm that would result from the killing, no matter how humane, would consist in the fact that the individual is prevented from seeking further pleasure that could have been experienced in a normal life. It is at that level that self-awareness provides a significant distinction between the interests of pigs on the one hand, and primates and humans on the other, and that distinction is acknowledged even by the most dedicated defenders of animal rights.

Consider, for example, the motivations of Tom Regan - perhaps the most renowned animal rights advocate - to condemn the use of a baboon to save the life of Baby Fae⁵⁰. Regan claimed that the baboon was the 'other victim' because the animal was not indifferent towards whether it kept its heart or not. Regan argued for the fact that the baboon had a life to live and reasoned that the duration and quality of that life mattered to the animal. In considering that animal as a 'subject-of-a-life', instead of an object that is subjected to indifferent living, he constructed the idea that it has the right to be treated with respect and, consequently, the right to enjoy its independent life without deliberate interference from human moral agents. That argument constitutes the basis to counter utilitarian calculations that assign value to an animal's life in terms of the net aggregate benefits that can be obtained from utilizing that life. The latter approach would, for instance, imply that the killing of one pig could provide sufficient organs to save the lives of six humans⁵¹ and thus would thus enhance the total balance of respect for the interest to pursue pleasant experiences. While Regan disallows a trade-off of an animal's right to life for greater benefits, he does acknowledge that the degree of respect due to the interest of an independent life varies depending on the kind of animal. When considering a lifeboat thought-experiment where we must sacrifice one of four normal adult humans or one dog, Regan acknowledges that it would be unreasonable to deny that the death of the dog would be as great a harm as the death of any of the four humans⁵². The *unequal consideration* of an interest to enjoy one's life is justified in relation to an *unequal interest* to enjoy one's life.

The dilemma that originates from the need for alternative sources of organs, cells and tissues, also constitutes a type of lifeboat scenario: in order to save the lives of humans on the waiting list for xenotransplantation, pigs must be thrown overboard. The notion of self-awareness can be more specifically applied as a guarantee that the lives of self-aware

humans are qualitatively superior to those of the merely sentient. It is on that basis that most animal rights theorists - who will nonetheless persist in emphasizing the interest of all sentient beings to experience the most joyful life possible - will believe that pigs cannot suffer from death to the same extent that humans can. Pigs, although they may have a form of self-awareness, are not persons and cannot be harmed to the extent that persons can. The distinction between persons and non-persons, as indicated by the Nuffield Council, is related to the notion of a biographical identity. Persons have an interest not merely in the experience of pleasant over negative experiences, but also in actively pursuing such experiences in the future. The precondition of having an interest for that future is that one can conceive of oneself as existing into the future and is able to initiate action in pursuit of long-term goals. Those conditions far exceed merely sentient self-awareness.

The argument that it is acceptable to grant unequal consideration on the basis of the presence or lack of this 'life journey interest' can be based on both quantitative and qualitative evaluations of the good of the interest. A utilitarian will be inclined to consider the total balance of joy experienced by both persons and nonpersons. In that sense, persons have considerably greater joy than nonpersons, as the *planning* of a life journey itself, the striving for certain goals, relates to *many* (if not, most) of our greatest joys⁵³. In qualitative terms, the experiences of a life journey are of *superior* value because persons are not indifferent towards the choice between living one's long-term life plans or living shorter spans of lives, even if the aggregate duration and total net welfare is equivalent in both cases⁵⁴.

Dispute may remain whether each of those accounts (along with many other alternative constructions) can completely preclude the possibility that persons are to a certain extent also replaceable. Nonetheless, much less disagreement will arise in considering that, to the extent that pigs lack such a biographical consciousness (which we assume they do), the greater interests of persons can outweigh the harm to the pigs. The greater interests of persons with regard to xenotransplantation relate to an increase in the total amount of pleasure of existing persons (waiting list patients) by saving them from premature death. An alternative view that focuses on increasing the total amount of pleasure for the pigs, regardless of the effect on the welfare of persons, but is much less compelling. One could perhaps claim that:

The pig has a stronger interest than anyone in the demand for xenografts. If there were sufficient human grafts, there would be no pigs at all.⁵⁵

This argument is sensitive to the suffering of sentient beings, but reduces that sentience to an interchangeable receptacle of experiences. However, the 'stronger interest' of the pig is dependent on whether or not its shorter life span does provide more pleasure than suffering. To equate the total proportion of welfare of a pig's natural life span to the combined welfare of various pigs with shorter life spans the additional burdens xenopigs may endure must be taken into account. It is conceivable that a creature would have been better off never having existed and is thus harmed by being brought under existence rather than that it offers a welfare 'replacement' of the pigs that have been killed for xenotransplantation before.

An argument could be made that xenopigs live and die under much more comfortable, humane circumstances and do not have a 'bad bargain' in comparison with pigs raised for agriculture or other forms of industry, or even compared to pigs in the wild, which are subjected to nature's cruelties. However, it is unclear why the condition of animals that are brought into existence to specifically serve human purposes should be compared to the condition of those that are not⁵⁶. Moreover, reference to *worse* conditions of other domesticated pigs may demonstrate the need to enhance the conditions of farm animals rather than proof that the conditions of xenopigs are acceptable. It does nonetheless seem reasonable to accept that the 'greater good' may to some extent even outweigh the harm to the pigs during their upbringing, unrelated to their death. From that perspective, Singer compares the suffering of animals in the food industry with the benefits people derive from eating them. He concluded that the discomfort and pain suffered by farm animals was not counterbalanced by the benefits for humans, which are purely of an aesthetic and nutritional nature⁵⁷. Conversely, he argues that nonpersons can be used in those cases in which that use would give rise to more good than harm: the use of animals to *save* human lives would be permissible, whereas their use to produce nonvital products would be contestable. In that sense, the direct benefits of using xenopigs to save the thousands of waiting list patients, overrides whatever interest the pigs may (consciously) have in preserving their life, particularly if the most measures are taken to maximize the pig's quality of life and to kill it humanely. Where precisely we draw the line in resolving the conflict between the welfare of persons and nonpersons will itself be a matter of dispute⁵⁸. Nevertheless, the ethical burden of proof lies on the side of those who argue that harm done to animal welfare is clearly outweighed by good consequences.

6.5 Conclusion

We have identified several common justifications for the use of pigs as source animals. Although the many arguments we have considered make a very convincing case against the use of nonhuman primates, they do not as such make way for the unproblematic use of pigs instead. First, the practical reasons for using xenografts from pigs instead of primates underestimate the many stumbling blocks concerning safety and effectiveness. Moreover, the most common moral justifications rest on presumptions that themselves need further discussion or clarification. As such, it will not suffice to simply refer to the tradition of slaughtering pigs for human purposes. Nor will it be sufficient to ensure that the instrumental use of a large amount of animals will not threaten species survival. And preferring the use of pigs to primates merely on the basis of human-like, familiar characteristics, is no less speciesist than excluding chimpanzees from moral concern on the basis of lack of certain human-like characteristics. In fact, it is a ‘speciesism by proxy’. The question should be which characteristics are ethically relevant and focus is then rightly shifted to the capacity to suffer. In establishing that nonhuman primates can suffer significantly from the psychological harm associated with xenotransplantation, it would be wrong to feel reassured that pigs couldn't. Nevertheless, there are sound arguments that do not undervalue the suffering and harm done to the pigs and at the same time provide reasonable justifications of those harms. Ultimately, those arguments rest on a trade-off with pertinently greater harms.

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PART FOUR

PATIENT RISK/BENEFIT AND THE HARM PRINCIPLE

7 Eliminating the risk of secondary xenogeneic virus transfer

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Abstract

The transplantation of porcine organs to humans could in the future be a solution to the worldwide organ shortage, but is to date still highly experimental. Further research on the potential effects of crossing the species barrier is essential before clinical application is acceptable. However, many crucial questions on efficacy and safety will ultimately only be answered by well-designed and controlled solid organ xenotransplantation trials on humans. The question then rises of what conditions are necessary in order to resume clinical trials if risks of PERV-transmission cannot be excluded through pre-clinical models. An alternative means of overcoming the safety and ethical issues is: willed body donation for scientific research in the case of permanent vegetative status (PVS). In this chapter the argument will be presented that conducting trials on such bodies with prior consent is preferable to the use of human subjects without lack of brain function.

7.1 Introduction

According to the Eurotransplant International Foundation - the second largest organ procurement system in the world - the demand for organ transplantation continues to grow at 15 per cent per year¹. The increase is likely to persist because of the shortage of human donors and the fact that improved technical skills and anti-rejection medication make transplantation an advisable treatment for more and more disorders. The lengthening waiting lists have compelled experts to search for an unlimited source of organs for transplantation. According to some, that is exactly what xenotransplantation has to offer in the near future.

‘Xenotransplantation’ refers to the practice of transplanting, implanting, or infusing living cells, tissues, or organs from one species to another. The term can also imply the *ex vivo* contact of bodily fluids, cells or tissues between different species². In what follows, we will mainly address xenotransplantation as the transplantation of a solid organ graft from pigs to humans for orthotopic (life-saving) use.

The procedure is still highly experimental. To date no experiments of solid organ xenotransplantation on humans can be called successful. While a few transplantations of porcine islet cells and foetal neuronal cells have taken place during the past ten years, immunological adverse reactions of xenograft organs have limited the best survival rates of recipients to a few months (with the exception of one case of nine-month survival)³.

For that reason and along with the fact that in the past several questionable clinical trials have been conducted (including the Baby Fae case)⁴, xenotransplantation has often appeared in a bad light. In past attempts to override the cross species barrier, xenotransplantation researchers have had to deal with a long list of objections. Those include objections based on religious constraints, legislation, emotional aversion, the rights and welfare of animals, the financial interests of stakeholders, uncertainties concerning the safety of the procedure and the high costs that are involved. Although all of those problems are important, the scope of this paper is limited to questions regarding the safety of the procedure, as this is to date the main challenge to progress in the clinical application of solid organ xenotransplantation. We will argue that experimenting on permanent vegetative status (PVS) bodies with prior consent has important advantages with regard to safety and ethical issues.

7.2 Safety issues

Over recent years, most medical attention has been focused on problems to overcome immunological barriers. As detailed in the fourth chapter, genetic manipulation of the source animals allows for the elimination of a certain porcine gene or the insertion of particular human genes so as to prevent the human immune system from activating hyperacute rejection. Nevertheless, there are other forms of rejection that still need to be overcome and of which the pathogenesis is not yet fully known⁵. Several researchers believe that those forms of rejection can be overcome by new immunosuppressive agents or by additional genetic modification of the source animals. So far this has not been established. In addition, many physiological incompatibilities between the widely divergent species are yet another series of problems that remain largely unexplored⁶. It is therefore highly questionable whether a genetically engineered porcine organ will one day support the life of a human.

Moreover, ever since Patience *et al.* provided evidence that variants of porcine endogenous retrovirus (PERV) could infect human cells⁷, the issue of potential transmission of infectious agents to a human recipient has repeatedly been raised in discussions on safety. Proof has been gathered of *in vitro* in co-culture human cell line infection by at least three variants of the provirus⁸, and recent studies have elicited infection of certain nonhuman primate cells⁹. Furthermore, one *in vivo* model has been shown prone to PERV infection¹⁰. *In vivo* studies in nonhuman primate models showed no evidence of PERV infection¹¹. There is also no proof of humans infected after limited exposure to porcine cells^{12,13,14,15}, although persistent microchimerism has been shown many years after exposure¹⁶.

At time of writing (2003), few data address the degree of risk for a new viral infection through xenotransplantation. Recent research does seem to point out that that risk is lower than previously thought^{17,18}. Extensive lists have been designed of possible pathogens resulting from a xenograft implant and sensitive assays have been developed to detect potential endogenous and exogenous viruses that may remain in the carefully bred specified pathogen free swine¹⁹. Nevertheless, some scientists have stressed that one can never be certain whether or not an organ is carrying a dangerous virus, due to the fact that some viruses may be unfamiliar, or latently present²⁰. The post-xenotransplantation infection results already obtained are mainly acquired from tests on isolated cells - no long-

term survival of a whole organ xenotransplantation model in humans has been obtained - and are thus restricted. Therefore the peril of unleashing a new epidemic through xenotransplantation remains. The fact that the techniques sought to prevent xenograft rejection lower the barrier for transmission of disease²¹ and that genetic modification of pigs may cause adaptation of the animal viruses²² support this fear. It has also been argued that the complete removal of PERV via selective breeding and knockout technologies is difficult, as multiple copies are present in the DNA of all porcine cells²³.

7.2.1 Moving ahead

Both in the UK and the USA, oversight agencies are nonetheless willing to further pursue xenotransplantation research. It is indeed conceivable that we are overestimating the magnitude of the problem. As we cannot currently predict the consequences of transplantation of a transgenic porcine organ into a human, we must also bear in mind the possibility that no transmission of dangerous, uncontrollable viruses will occur. In that case, many would find it immoral to deny the possibility of a life-saving intervention if it is one day thought feasible. It would be questionable to still allow transplant teams to increasingly rely on problematic strategies to widen the donor pool, such as the use of organs from so-called marginal donors. The use of organs from elderly donors²⁴ and donors with a health condition^{25,26} is not an attractive alternative to the prospect of transplanting compatible, healthy porcine organs. Safe and effective xenotransplantation would not only resolve the current allograft shortage, it would also annul the high financial and emotional burdens associated with long waiting times for an available donor organ and allow for a precisely scheduled transplant, thereby overcoming many practical problems for the transplant team. Also, specially engineered pigs may one day provide suitable organs for infants, for whom the organ shortage is the most devastating.

7.2.2 Proceeding with limited xenotransplantation trials and experiments involving human subjects

Research restricted to tests on infected human blood samples in controlled laboratories cannot cover all possible consequences that viruses may have on living human bodies. That is also the case for *in vivo* animal models, although they do form instructive opportunities for basic research. Even trials on nonhuman primates, although assumed to produce the

most convincing results due to the great genetic similarities with humans, cannot produce conclusive results given the fact that both species react differently to certain viruses. Large-scale use of primates as experimental subjects is also ethically very problematic, precisely because of the great similarity to humans, not only genetically but also on a cognitive and emotional level.

Further progress in pre-clinical studies is necessary before clinical trials of solid organ xenografts can be reconsidered. Nevertheless, it is well established that many crucial questions on efficacy and safety, including those regarding the side effects of immunosuppressive drugs, the presence of infection and features involving the physiological interaction between the xenograft organ and the host, will ultimately only be answered by well-designed and controlled solid organ xenotransplantation trials on humans²⁷. On which conditions, given the risks and ethical issues involved, such clinical trials should be resumed in due time, is the question we will examine in what follows.

7.3 A proposal for body donation in case of cortical brain death

7.3.1 Living human subjects

Proceeding with limited experimentation and trials on human subjects will ultimately be the inevitable step in order to investigate the consequences that the advanced xenotransplantation procedures may have on a human body. Although that research will ultimately depend on experimentation involving living human subjects, it is not an ideal starting point. As the Council of Europe has recently suggested, such clinical experimentation must first have evident therapeutic benefit to the recipient and exclude all risks to public health²⁸.

In the case of xenotransplantation, it is conceivable that certain individual transplant patients, facing death, will express their voluntary willingness to participate in new clinical trials of xenotransplantation, even if therapeutic benefit is not fully established. Such prospective trial participants may have little chance of surviving if they are not given an alternative to allotransplantation, and may therefore find the unknown consequences of the xenotransplant acceptable. However, such a situation would be most problematic.

For one, as the risk of unleashing a pandemic outweighs the benefits to the individual recipients, that would violate one of the most basic medical norms requiring a balance between the predictable risks and burdens and foreseeable benefits to the subject or to others²⁹. Moreover, some extreme measures would be required in order to protect public health, and some of these conflict with the rights of human experimental subjects as well as with some basic human rights. Because of the ill-defined risks, future experimental xenograft recipients will have to consent to possible constraints of monitoring and to precautionary measures that restrict social and personal contact. Minimally, the first new recipients will be asked to permit long-term monitoring along with indefinite testing and preservation of samples³⁰. Attempts to trace and study possible unknown viruses - let alone to control real outbreaks - are however lacking when limited to collecting blood and tissue samples. Most guidelines therefore include the prerequisite that relevant contacts must be informed about the experimental subject's status of xenograft recipient, above all those who are submitted to possible contact with their bodily fluids. Especially cautious measures will have to be observed with respect to behaviour towards sexual partners, who will probably be required to undergo regular testing as well. The recipients will perhaps also be advised against having children. In extremis, if contagious infection does occur, the surveillance could go as far as placing the experimental subjects in solitary confinement for an indefinite time, allowing almost no exposure at all³¹.

Even with the awareness that precautionary measures of that kind are necessary from the perspective of public health matters, it is hard to see how such drastic measures may be imposed on the subjects. That many of the suggested restrictions are difficult to justify, is an opinion articulated in an early report by the Nuffield Council³². When considering some of the harsher constraints, the recipient is not merely inflicted with the physical risks of infection and of immunological harms, but also with a denial of significant psychological interests. At stake here are intrusions of the right to non-interference in personal affairs and private life, the protection of confidential information, and - in the theoretical case of isolation - the right to liberty. According to the Council of Europe, violations of those rights are justifiable: "(...) for the prevention of the spreading of infectious diseases (...)" and "as is in accordance with the law and is necessary in a democratic society in the interests of (...) public safety (...), for the protection of health and morals, or for the protection of the rights and freedoms of others"³³. It is precisely for the protection of the rights and freedoms of others that quarantine measures are imposed in cases of natural virus outbreaks. Nevertheless, requiring a prospective xenograft recipient to consent to such restrictions of his or her rights even before there is evidence of a health hazard would

involve a setback of significant psychological interests for the recipient - and conceivably, to the close contacts in his or her social environment as well. Ideally, the interests of the research subjects are the prime consideration. The trials should enhance the patient's quality of life, not impose an extra burden.

Besides that, genuine problems arise concerning the requirement of informed consent. First, in no way can the recipients be fully informed of the possible consequences of the experiment, due to the fact that the possible effects are unquantifiable. Second, given the likeliness that the participants to such trials will be driven by despair, doubts may arise regarding the voluntariness of their participation. In addition, it is not unthinkable that the patient will disagree with his former consent over time. The consequences of a participant's decision to withdraw from the research after the experiment - a basic right formulated in the Declaration of Helsinki³⁴ - would be drastic. Finally, the requirement of consent is already complicated enough regarding individual patients; in that case it would call for plural consent from close contacts and possibly even public consent. Although attempts to achieve public consent have recently been made³⁵, it is clearly quite hard to attain for individual experimental cases of xenotransplantation.

Summarizing, xenotransplantation trials on living human subjects would intrude upon generally accepted ethical codes and rights regarding experimentation on humans. Those guidelines can all be grasped by the norm that the physician must "(...) protect the life, health, privacy, and dignity of the human subject"³⁶. Presuming that the alternative to xenotransplantation is a valuable one, however, the concern about the loss of the substantial knowledge that could be gained from experimental trials must remain. Future clinical trials of xenotransplantation must first and foremost be safe and in conformity with ethical principles. If this is not feasible, alternative means of obtaining information about human bodily reactions to long-term xenograft exposure are necessary. In what follows, we will explore and examine the possibilities of experimenting with human subjects who can neither be harmed by the side effects of the experiment nor be an infectious hazard to others.

7.3.2 Living human bodies

From a research perspective, the most instructive situation would be the acquisition of sufficient data from non-therapeutic experiments on biologically active human bodies.

From an ethical perspective, on the contrary, the need to protect the physical and psychological wellbeing of the subjects and the broader community is of paramount importance. Given those discordant interests, experiments should ideally be conducted on humans who, although alive in the biological sense, do not suffer from health risks or restrictions on their personal and social life. That means that the ideal research subjects should lack the essential aspects of human existence to which human rights and medical-ethical principles are attributed, while they are nonetheless biologically active.

In this respect, it could be argued that such living bodies are comparable with the bodies of the brain dead and one could thus suggest the use of brain dead bodies as research subjects. Brain dead bodies - 'living cadavers', as they were once called³⁷ - are bodies with total loss of brain function that are connected to a mechanical ventilator that sustains some somatic functioning. Conducting xenotransplantation experiments on the whole brain dead is conceivable, as it is technically possible to transplant porcine organs in such bodies, while the basic bodily functions - such as breathing and steady blood flow - are artificially maintained. From an ethical point of view, that would be an attractive situation because it would enable complete examination of the xenotransplantation effects. It would also drastically minimize the risks of contagion from possible viruses, as the bodies experimented on could be quarantined for an indefinite time. That situation would be preferable to the use of living patients, given that a brain dead body, lacking the sentience of its biological existence, cannot suffer from the otherwise psychologically distressing constraints nor from the physical consequences of the transplantation. Research would evidently benefit from those experiments, as they could increase our understanding of potential viral infections and immunological reactions without putting the population at risk. That advantage could be optimized if it were then decided to halt all other trials of xenotransplantation until the results of those small-scale trials were evaluated.

There are however practical problems with such a scenario. With whole brain death, relatively no significant bodily function will work on its own. The techniques used to keep basic bodily functions working may prove sufficient to keep organs and tissues from deteriorating; they do not ensure a relatively normal bodily reaction to the xenograft. Moreover, the mechanical devices designed to keep the body biologically active cannot continue doing so indefinitely, perhaps not long enough to ensure the absence of latent viruses.

Are the ideal experimental subjects of the sort described purely theoretical, then? One cannot help but think of ‘patients’ who are in a permanent vegetative state (the very word ‘vegetative’ implying that these are bodies in such mere biological existence), a state that can last for many years until it results in biological death.

As defined by Jennett and Plum³⁸, the vegetative state is a clinical condition of profound brain damage that is characterized by both a loss of awareness and preserved arousal. In the literature, there is not much clarity on the term as the distinction between vegetative state, persistent vegetative state, and permanent vegetative state is often neglected. The Multi-Society Task Force on PVS has attempted to provide us with better delineated stipulation, employing the term ‘persistent’ to describe those cases in which the vegetative state lasts for more than one, three, or 12 months, according to aetiology; whereas the term ‘permanent’ is used to imply the irreversibility of the condition³⁹. It is the latter meaning, characterized by irreversible abolition of consciousness, we wish to address here.

With the term ‘*Permanent Vegetative State*’, we refer to a state in which *all* functioning of the cerebral cortex - the core of consciousness - is *permanently* lost, and yet the brain stem (or parts of it) is still working. It is marked by preserved autonomic and vegetative functions despite irreversible mental impairment. Reflex motor actions such as spontaneous eye opening, yawning, chewing and grimacing still occur, as well as spontaneous respiration and physiologic features of sleep and wakefulness. Nevertheless, a patient having lapsed into a PVS lacks awareness and cognition, which is apparent in, for example, the inability of purposeful, voluntary, and reproducible responses to stimulation⁴⁰. Precise information on the prevalence of PVS is lacking, but studies show that the condition occurs fairly regularly. Estimates indicate that in the US alone there are between 10,000 to 25,000 adults and between 4,000 to 10,000 children in PVS⁴¹.

Due to the fact that spontaneous breathing and reflex motor actions remain present, it is counterintuitive to think of these patients as dead. At present, our society emphasizes the irreversible cessation of all brain functions as the main criterion for diagnosing death. However, debate on this criterion has been ongoing since the standard of whole brain death was proposed by the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death in 1968⁴². Robert Veatch was a pioneer in challenging the need of total lack of brain function and stressed the importance of sentient and socially interactive existence⁴³. No proposals concerning a higher brain death criterion have been

legally endorsed as yet and therefore a body in PVS is still statutory a living patient. Still, one could argue that even the term 'patient' is inappropriate in relation to the condition, because the word generally refers to a living person, while a body in PVS has permanently lost all forms of personhood. Regardless of the ongoing dispute on what constitutes personhood, a precondition to be a person is the capacity for cognitive and affective mental functioning, which is inextricably bound with the notion of awareness. The parts of the brain that are crucial in terms of the mind and sentient existence are irreversibly lost in a PVS body. The organism can no longer experience pain and pleasure nor any other feelings; it does not have any awareness of the environment or the self and has no capacity for information integration. PVS bodies have no interest in maintaining their biological life, nor do they value it, as they have permanently lost the capacity to acquire values. That is in fact the idea behind former case specific court approvals for the removal of feeding tubes: they acknowledge the fact that the PVS body has no interests in treatments it may or may not receive. Likewise, one could argue, it is of no interest to a PVS body whether the body is involved in clinical xenotransplantation trials or not, as it can neither benefit from the advantages nor suffer from the disadvantages that are associated. Having no capacity for any mental activity whatsoever and thus left in a state of complete unconsciousness, it is reasonable to say that in fact a PVS body has no interests at all, a rationale often rehearsed in the literature.

Of course, the idea we are suggesting here is not entirely new. Over the past years, some philosophers have defended the opinion to legalize the use of organs from cortically dead bodies for transplantation⁴⁴. Proponents have argued that it is 'intrinsically moral' to use the organs of anencephalic neonates, who lack functioning cerebral hemispheres, as that would allow some good to come from their tragic situation⁴⁵. They claim that the lives of other children could be maintained, while at the same time a meaning is given to the short and non-sentient existence of the anencephalics. In fact, the American Medical Association's Council on Ethical and Judicial Affairs briefly took that position as early as 1988⁴⁶. Several philosophers apply similar argumentations in favour of organ retrieval from PVS bodies once the decision has been made to allow those bodies to die through withdrawal of all treatment⁴⁷. The arguments appealed to are based on a conviction that such bodies are irreversibly non-sentient and non-cognitive and thereby have no interest in being biologically maintained, whereas their organs could save the lives of many.

Regardless of the intention of the authors, one could logically derive from their suggestion concerning retrieval of organs for transplantation purposes the idea that it is permissible

to treat PVS bodies the way we currently treat the bodies of the whole brain dead. Based on the idea that PVS - if established that the decisive brain damage is permanent - implies the death of the person, we are of the opinion that not only the donation of organs but also of the entire body for scientific research should be permissible for PVS bodies on the condition that former consent has been obtained. Moreover, while potential organ donations from PVS bodies would increase the amount of donor organs available, they will still fall short in meeting demand and will thus be of limited value. By contrast, the implications of willed body donation in case of cortical death for xenotransplantation related research are far-reaching. As the autonomic and vegetative functions of PVS bodies can often be maintained for years, their use would allow the opportunity to fully test the long-term consequences of a solid organ xenotransplantation. This can potentially contribute to the progress necessary before large-scale clinical application to a potentially *unlimited* number of recipients can be considered.

7.4 Discussion: the unbearable lightness of not-being

The suggestion offered here raises several questions. Ultimately, it is about consented donation of the body to science in the case of cortical brain death. In our view, the following major concerns remain: (1) the need for certain diagnosis of the irreversibility of the state; (2) the need for sufficient and relevant functioning of a body in PVS; (3) the need for prior and informed consent by the person ending up as a PVS body.

(1) The problem of establishing the irreversibility of loss of cognitive capacity is often cited. Although diagnostic certainty of cortical brain death is an indisputable prerequisite for our suggestion, dispute exists over the ability of scientific medicine to achieve that certainty. PVS is taken to be essentially permanent three months after non-traumatic and twelve months after traumatic brain injury⁴⁸. However, rare reports exist of recovery with moderate disability after non-traumatic PVS lasting eighteen months and traumatic PVS lasting for thirty-six months⁴⁹. Recent research suggests that therapies can be designed to induce 'patients' to emerge from PVS⁵⁰. There is still disagreement over whether exceptional cases of 'awakening' are due to a lack of diagnostic certainty or whether they are just incidents of misdiagnosis. It is indeed a challenge to ensure complete and irreversible loss of capacity for consciousness, because the diagnosis depends on providing evidence of a negative, an absence. However, beyond a certain point, hope for bringing back the most rudimentary form of consciousness is gone. New techniques are constantly

being developed to specify that point with accuracy. Positron emission tomography⁵¹ and studies on the magnetic resonance of the brain⁵², among other things, are important efforts in understanding the neural processes underlying the vegetative state. If in the future such techniques prove to be reliable, then we could be certain that the experiments we are suggesting would be limited to bodies that are demonstrably irreversibly cortically destroyed.

(2) A second possible obstacle to the realization of our proposal is that it may be discovered that a body in PVS, and in particular the immune system, does not sufficiently function like a normal body with unaffected brain functioning. If so, there would be no reason to prefer our scenario to the use of animal models, as neither approach would attain the compelling conclusions on the safety of the procedure. However, at present there is no clarity about that. Were this to be the case, then our suggestion would indeed be useless within the framework of xenotransplantation trials, although it would still make sense for many other forms of scientific research.

(3) If it can be accepted that PVS bodies can be regarded as dead, then experimenting on them is legitimate under the same conditions as experiments on cadavers. Training and refining invasive technical skills on cadavers or newly deceased patients is not an uncommon practice in medicine due to a lack of suitable educational alternatives for those procedures. Multiple surveys have shown that the general public does not disapprove of that method⁵³. It is generally deemed ethically acceptable when perceived as an educational opportunity that will benefit many patients dependent on the technical, life-saving skills practiced. However, as a substantial prerequisite of all scientific research on human bodily material, former consent would be necessary to ensure that the experiments are not conducted against the personal wishes of the deceased person. Registering a 'living will' is a means of ensuring that the right to self-determination is respected after death.

An additional argument in favour of allowing the donation of one's body for scientific experimentation in case of a permanent vegetative state, can be drawn from some people's refusal to grant that a cadaver and a dead person may be treated alike. Over the past century, we have gone a long way before acknowledging that whole brain death (also formerly described as 'hopelessly unconscious patients'⁵⁴) is a sufficient condition of death of the individual. However, much controversy over the legitimacy of that concept still exists today. It has been suggested that the concept of death is not inextricably bound with the criteria of whole brain death. Debate exists, for instance, on the equation of

brain death to the cessation of integrated functioning of the entire body⁵⁵. There is also evidence that weakens the idea that there is a total absence of all brain function at the moment 'whole brain death' is determined⁵⁶. In contrast with what the term presumes, the declaration of whole brain death is in medical practice often based on the irreversible cessation of particular brain functions, while other brain activity - deemed irrelevant in deciding whether a person is dead or alive - remains. It is the death of the brainstem that is the decisive criterion because all higher brain activity is assumed dependent on lower brain activity (and that suggests that there is a tendency to think less of the lower brain functions in terms of defining life and to emphasize the critical role of the higher, cortical forms).

It seems that there is still much conflict about what constitutes death, even among experts. Because convictions about death are not absolute, one might argue that in the end it should be left to the individual himself to choose the criterion/criteria of death he or she wishes to endorse in a living will. Robert Veatch formerly formulated that idea. He proposed to legally tolerate religious and philosophical objections to a uniform definition of death,

(...) a conscientious objection that permits patients to choose, while competent, an alternative definition of death provided that it is within reason and does not pose serious public or other societal concerns.⁵⁷

Veatch argues that it goes against the fundamentals of liberal pluralism to prevent individuals with dissenting religious and philosophical views from incorporating other definitions of death.

With regard to our suggestion, a testamentary will relating to postmortem research is required, allowing an individual to indicate the concept(s) that best corresponds to the individual's own concept of death (be it cardiopulmonary, whole brain or cortical brain death). Such a will would also allow a person - keen to help science - to stipulate his or her wish to donate the body or certain bodily materials to science in accordance with that concept of death. In the latter case, one could - should one desire - specify the type of research he or she wants to participate in. In that way, one could, for example, opt to participate in the xenotransplantation trials discussed. Information could be provided to instruct those interested in the different types of research and the consequences they will have on the body. Perhaps such a deliberately expressed wish could be recorded on identification documents or in a whole body donor registry.

Some important questions remain when considering allowing people to donate their body to science in accordance with individual conceptions of death.

Firstly, it may be put forward that the general public will not welcome such a shift in policy. If permitting willed body donation in case of PVS implies that we go against some of the most fundamental convictions on life and death matters held by relatives, physicians, and the general public, our suggestion could cause public distrust and outrage. However, studies on public attitudes show conflicting evidence. On the one hand, reports on organ donation indicate continued discomfort among respondents - including physicians - over the equation of whole brain death with the death of the patient⁵⁸. On the other hand, several studies suggest rather unconventional attitudes towards cortical brain death. One American study showed that 89 per cent of respondents thought it ethical to withdraw life-prolonging treatment in cases of PVS and almost two thirds held that it is ethical to use the organs of PVS bodies⁵⁹. Besides that, no consensus on what constitutes death is required in order to implement our suggestion, as the emphasis is on personal beliefs.

Secondly, it may be suggested that conducting experiments on PVS bodies is disrespectful of the deceased person, because invasive procedures and mutilating treatments would be applied. However, such experimentation on cadavers is deemed acceptable under certain circumstances. If similar conditions are met in the case of PVS and if prior consent is legitimate, experimenting on PVS bodies is no more disrespectful than current postmortem research. Also, assuming that a deceased person has no interests (our argument for allowing experimentation to be conducted on PVS bodies in the first place), one could conclude that a PVS body likewise has no interests in whether or not its prior wishes are respected. Deciding to acknowledge the personal wishes as expressed in a will in spite of that, speaks in favour of respect for the dead. The same cannot be said of all postmortem research conducted today. There have been various indications that some hospitals retain body parts after death for medical or research purposes, without prior consent or discussion with the next of kin. Moreover, the type of willed body donation that we suggest here is not just respectful of the wishes of the deceased; it also promotes other values, because use is made of the body to increase medical knowledge and help others.

A final issue concerns the question whether decisions regarding the scientific and medical use of the body are ultimately restricted to the person who died or whether relatives or other parties involved are entitled to decide. That is a topical concern. Recent literature

reports that most adults believe that consent from family members prior to practicing procedures on the newly dead is advisable^{60,61}. New Zealand is one country that has legally enforced the right of a formal family veto to override the deceased's directive in relation to retention of body parts⁶². The arguments highlight the enduring interests of others after death. It is important to consider the effect PVS body donation would have on the family. With regard to our suggestion, one could indeed claim that while the suffering of the PVS body may not be at stake, the relatives are emotionally involved in the way the body is treated and, as such, should have a say in the matter as well. As a PVS body is not a corpse ready for burial, it is conceivable that conducting experiments on it will be very distressing to them.

When considering the interests of relatives, a similarity as well as a distinction can be drawn between donation of a cadaveric body and of a PVS body for scientific purposes. Both practices are comparable in that the disposal of the bodily remains is uncertain. That implies that either the two practices should be equally condemned, or equally permitted. The main difference, however, lies in the fact that the scientific or medical use of the warm bodies of deceased persons (higher cortical or whole brain death) evokes entirely different emotional reactions compared to the use of a "cold" cadaver.

In spite of that emotional distress, there are many cases where the testamentary wishes of an individual take priority over the emotional involvement of the family. In many countries, for instance, advance directives concerning end of life decisions (both refusal of treatment and - as in Belgium and the Netherlands - request for actively ending the life) of those who become permanently or even irreversibly unconscious are respected regardless of the objections of relatives. As persons who are irreversibly unconscious or 'dead' no longer have any interests, one could in principle argue that testaments - of any kind - have no stringent power. Nevertheless, it is generally accepted that the transfer of property and patrimony and the wishes concerning end of life decisions or preferences with regard to burial, are arranged according to the terms of a will. The precise intention of having a will is to ensure that an individual's wishes are followed, even if that person no longer has a stake in his wishes being followed because he no longer exists in that sense. In the case of PVS body donation, relatives may even be helped by the fact that the deceased has stipulated his wish to body donation in case of cortical death. They may be consoled by the altruistic nature of the donation and by the fact that body donation is something the deceased deliberately chose.

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8 Xenotransplantation and the harm principle: factoring out foreseen risk

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Abstract

Xenotransplantation - the transplantation, implantation, or infusion of live cells, tissues or organs from a nonhuman animal source into humans - is being considered as an alternative strategy to alleviate the shortage of human grafts. The pursuit of this technology is nonetheless restricted by an unquantifiable risk that the use of animal grafts will unleash new zoonoses that may affect the public at large. In this chapter we will demonstrate that the regulatory measures taken to prevent secondary infections, currently do not warrant full-blown protection of public health. This reality forces us to reconsider the extent to which the public should be guaranteed protection from a xenotransplant-related health hazard. In pondering that question, we will suggest that the permissibility of health hazards posed by emerging (bio)technologies is dependent on the perception that the benefits are both substantive and attainable and on the duty to account for foreseeable risks. In that sense, there is both good and bad news for the acceptability of xenotransplantation. An increased understanding of the infectious agents that are known to pose a health risk, allows to relate the man-made health threat to risks that have a natural origin. Even if it is eventually possible to exclude all foreseeable risk factors, however, the onus for those wishing to implement xenotransplantation procedures in the clinic lies in demonstrating greater proof of the benefits which they have long promised to provide.

8.1 Dealing with the risk of a xenogeneic pandemic

The possibility of infecting patients with either recognized or novel infectious agents transmitted from xenotransplantation products is perhaps the most important argument restricting clinical use of xenotransplantation practice.

It is well established - and topically illustrated by the recent outbreak of H5N1 Avian Influenza - that nearly all of the infectious diseases that have emerged over the past decade can be traced to animal-derived viruses, bacteria, or prions that have passed onto or adapted in human hosts¹. Xenotransplantation appears to pose a particularly pertinent health hazard. That is due to the fact that transplantation bypasses most of the patient's usual protective physical and immunological barriers. There is also lack of knowledge about the behaviour of source animal-derived infectious agents in immunosuppressed humans. Moreover, the risk of xenogeneic virus transfer materialized with evidence that a family of porcine endogenous retroviruses (PERVs) can infect human primary cells and cell lines *in vitro* and can adapt to those cells by serial transmission on uninfected cells^{2,3}. In contrast to exogenous retroviruses, endogenous retroviruses are deemed particularly problematic because they are resident as proviruses in the DNA of the host, and thus difficult to exclude. Three classes of the infectious type-C endogenous retrovirus (PERV-A, PERV-B, PERV-C) were identified. Those classes share profound sequences homologies but are substantially different in the receptor-binding region of the viral surface *env* gene⁴.

In a cautious, initial attempt to define and determine the seriousness of the risk posed by the use of pigs as xenograft source animals, Patience *et al.* identified several questions that needed answering before we can decide whether xenotransplantation experiments on humans should proceed⁵. More knowledge was required in terms of the microorganisms present in the donor animals, the likeliness of cross-species microbe transfer to cause disease in humans, and the likeliness of and capacity for potential cross-species microbe transfer to elicit a human pandemic. Pending the answers to these questions, several pleas for a moratorium were made^{6,7,8}. In most regulatory authorities, however, a brief *de facto* moratorium in 1998-1999 in name of the precautionary principle has been replaced by stringent national oversight of adherence to detailed monitoring requirements^{9,10,11}. All regulations mandate that the source animals should be specified pathogen-free and bred in bio-secure environments. A thorough, ongoing system of infection detection is required during the entire process leading to and following clinical application. The detection

procedures will minimally consist of routine systematic collection, analysis, and interpretation of archive specimens taken from the source animals, recipients, close contacts, caregivers and medical staff. The surveillance requirements will impose lifelong constraints on the prospective recipients and possibly their close contacts. Some of those constraints may conflict with an individual's right to confidentiality, mobility and liberty¹². Among the more stringent requirements, it has been suggested that the prospective trial recipients should refrain from having children¹³. In the understanding that the risks of xenogeneic virus are not confined to the nation in which an outbreak initially occurs, great effort has been put to establish international cooperation for the protection of public health on a global scale. The Council of Europe¹⁴, the Organization for Economic Cooperation and Development (OECD)¹⁵, the World Health Organization (WHO)¹⁶, the European Agency for the Evaluation of Medical Products (EMA)¹⁷ and the International Xenotransplantation Association (IXA)¹⁸ have urged international collaboration to develop universal standards of good practice. Those institutes recommend that clinical applications of xenotransplantation are not to be carried out without effective national regulatory control and surveillance mechanisms and/or without specific authorization. Additionally, they mandate international harmonization of accepted norms for surveillance and data and require rapid exchange of scientific clinical information.

Many have questioned whether those measures are both a feasible and an acceptable means to restrict the propagation of xenogeneic infectious diseases. The need for long-term (potentially lifelong) monitoring will undoubtedly have an effect on the freedom and privacy of prospective xenograft recipients and their close contacts, who will also be asked to undergo testing. It is particularly unclear whether that is something we may demand from patients who aim to improve their quality of life¹⁹. Moreover, and given the high rates of non-compliance to health recommendations after an allotransplantation²⁰, it is unclear whether the consenting recipients would be continuously willing and able to adhere to the extensive and stringent supervision. Importantly, while consenting xenotransplant recipients would necessarily lose the right to withdraw from the research after the experiment, the legal means by which compliance can (and should) be enforced prior to a *demonstrable* state of public health emergency have not yet been set in place^{21,22}.

The feasibility of stringent xenotransplantation oversight is also undermined in reference to the trials that have been conducted without regulatory oversight in the past and those which slip through the net of international oversight today. Unless the patients who have already undergone a xenotransplant prior to the stringent regulation can be identified and

controlled, the risk of (latent) xenogeneic infection is out there. There are also verbal reports that pig-to-human transplant experiments are currently being conducted in countries without proper oversight^{23,24}. Those reports indicate that at least 400 islet transplants and 2,000 bovine cell transplants for pain relief have been conducted in China so far. In Russia, allegedly hundreds (possibly more than 800) of rabbit islet transplants have been done. That opens the door for the risks of ‘xenotourism’, in which case a patient may seek a xeno-‘therapy’ in those specific nations where they are available. The xenotourist may perhaps mistakenly assume that established oversight is in place, or be kept unaware of the potential dangers inherent in the unconventional procedures. It is therefore unlikely that such a patient will attune to appropriate precautions²⁵. An advisory group assembled by the World Health Organization suggests that such practices should be stopped²⁶. However, the means to do that are still lacking.

In light of those practical and ethical difficulties in preventing secondary infections, protection of public health is not guaranteed. That reality forces us to reconsider to what extent the public should be guaranteed protection from a xenotransplant-related health hazard. A re-examination of the duty to prevent public health harms is also encouraged by the increased optimism that the risk of xenogeneic viral infection is not as compelling as it was a decade ago.

8.2 Do as you wish, but do not make a nuisance of yourself to others

Xenotransplantation involves the conflict of two intuitively felt moral duties. By not pursuing xenotransplantation trials, we are refraining from helping waiting-list patients who currently have no alternative to life-saving treatment. In other words, we are potentially allowing preventable deaths. By pursuing xenotransplantation trials, on the other hand, we could help some individuals at the cost of harming (possibly many) others, with harm broadly defined as affecting someone’s interests adversely.

The above-mentioned approaches to exclude the possibility of virus transmission or proposals to ban xenotransplantation altogether, suggest that the duty not to harm others is the weightiest principle. That would seem to reflect the maxim “Above all [or first] do no harm” (*Primum non nocere*), which is sometimes (although incorrectly) deemed the essential principle underlying the Hippocratic tradition of medical ethics²⁷. Within a purely medical ethics context, however, the duty not to harm would not necessarily enjoy priority

over the duty to provide benefit. The principles serve as a guide for good clinical practice to patients and have a *prima facie* character rather than a definite hierarchy²⁸. Whether or not in a given situation the principle of beneficence overrules the principle of nonmaleficence is co-dependent upon two other principles: respect for persons and equitable distribution of benefits and burdens. In considering the role of those principles, it seems to matter whether the person to be harmed is the very same person who is to be the beneficiary or some other person.

In Kantian ethics, acknowledging a person's autonomy implies viewing persons as ends in themselves and not merely as a means to the ends of others. Each person merits respect for his or her 'private sphere', in which he or she is sovereign and free to determine his or her own destiny. As a moral notion to guide our acts, that implies that an individual with the necessary critical mental capacities to act as an autonomous agent may not be restrained by controlling interferences from others. Strong defence of personal sovereignty will grant autonomous beings the right to act in such a way that is of harm to them - even when the decisions are unreasonable or when they imply an alienation rather than fulfilment of autonomy - as long as the act is done voluntarily and knowingly of the effects²⁹. Milder trends towards anti-paternalism are more apparent in the medical context. A patient is generally assigned a right to consent to medical research or therapies that are potentially harmful to his or her health on the additionally specified condition that the risks are reasonable in relation to the potential benefits. From that perspective, we can imagine that a recipient will be willing to accept a xenotransplant, fully knowing of the potential of xenogeneic virus transmission. That harm may to a certain extent and in severe cases be counterbalanced by the benefits. Nevertheless, the least stringent and most basic limit of personal sovereignty is set to those harms that are also other-regarding³⁰. This is the harm principle introduced by John Stuart Mill:

The only part of the conduct of any one, for which he is amenable to society, is that which concerns others. In the part which merely concerns himself, his independence is, of right, absolute.³¹

The duty to respect the autonomy of others makes a strong case against the moral permissibility of secondary xenogeneic virus transfer. The case could also be made in reference to the fact that, for the general population, the harm of a xenogeneic epidemic will not be counterbalanced by the benefits. That is particularly compelling when placing the notion of just health distribution in a global context. The developing world, most parts of which lack even the most minimal health care, will not have access to the benefits of

that expensive technology (in effect, a critique against most high-tech medical therapies) but will rather be confronted with yet another health burden.

The conflict between the autonomy of the beneficiary and the autonomy of persons other than the patient being treated, could possibly be resolved if those others were to consent to the acceptability of the harm involved in xenotransplantation (perhaps, in the belief that they themselves may one day benefit from the therapy). However, consent of all those potentially involved in the harm at stake is virtually impossible, because in effect, the whole world is. In practice, seeking collective consent applies to public consultations on a national level. The important role of public input in the decision whether or not to proceed with xenotransplantation has indeed been endorsed^{32,33}, but so far, the various national efforts have not yielded unanimously positive acceptance rates. Rather to the contrary. Public consultations in Canada, the Netherlands and Australia resulted in overall recommendations not to proceed with clinical trials until the risks were better understood and could be better managed³⁴. When such nations decide not to engage in further trials, assurance that they will be protected from the harm they do not wish to accept is conditional, as the harms of infectious disease will not be restricted to the country in which the transplant is performed. In a sense, any country that engages in this research chooses to run the risks for everyone.

The moral weight of the harm principle is deeply engrained in our common sense morality. In fact, we will generally conclude that duties not to injure others are more compelling than duties to prevent harm or to provide benefit. A classic thought experiment often used to illustrate this is one in which we are asked to consider saving the lives of five patients on the waiting list by killing an innocent person in order to retrieve his or her vital organs³⁵. While that act would bring about the best consequences in terms of lives saved, most of us would object to the means by which the lives are saved. The moral impermissibility of such harm is not necessarily grounded in deontological principles: it can be supported on consequentialist grounds as well. The consequentialist could maintain that, although initially most lives are saved, killing a person for his or her organs would render the results worse overall. For instance, if the transplants were unsuccessful, the lives of all six people rather than five would go lost. Alternatively, if the killing were brought to light, the distress that could cause among the public would diminish the overall welfare. Moreover, if the public were to lose trust in the medical community and refrain from seeking medical help, that could result in the unnecessary loss of many more lives.

Notwithstanding this, even the duty not to harm others is not a moral absolute. Where the outcomes are clearly favourable in terms of overall results, this is a consideration to which even some deontic theories would not be entirely insensitive³⁶. In other words, the constraint against doing harm to others can be outweighed. The problem, however, is that opinions may vary regarding the point at which the harm is counterbalanced. There is no clear amount of benefit that must be at stake before the constraint against doing harm can be forsaken. Kagan indicates that the threshold is rather a function of the size and nature of the harm that has to be done to bring about the good results³⁷. The difficulty of balancing benefit and harm is further complicated in those cases in which we are not asked to consider the permissibility of doing harm, but only a *risk* of doing harm. The nature of the problem is highlighted by the fact that few of our everyday acts involve *no risk* of harming someone else. Some of those everyday acts - Kagan gives the example of driving cars³⁸ - imply risks of serious, life-threatening harm. That suggests that the permissibility of imposing risk of harm to others is not solely dependent on the nature and size of harm at risk, the probability that the harm will occur is also taken into account. The higher the risk, so it would seem, the higher the threshold.

Establishing the permissibility of risk seems highly intangible in the case of xenotransplantation. The number of people at stake in both benefits and harms is potentially large-scale, while the size and nature of the harm - whether it be a harmless influenza or a fatal pandemic, the range in between, or neither - and the probability that any of those scenarios will occur are essentially *uncertain* and *unquantifiable*. Given that the “scientific-descriptive” component of risk assessment is thereby lacking, we are compelled to make do with a second component, which involves an individual and social normative basis³⁹. In what follows, we borrow two analogies in an attempt to provide additional factors which play a role in the perception and acceptance of man-made public health hazards.

8.3 The ethics of man-made public health hazards

8.3.1 Analogies

In her account of the conflict of individual and public interests inherent in xenotransplantation, Martine Rothblatt compares the situation to the prior development of

two similarly risky biotechnologies⁴⁰. In both cases, the technologies harboured a great potential benefit and imposed risks of equally grave harm to the public. Nevertheless, the situations deviate in terms of tolerance of the risks. In what follows, we hope to shed light upon the permissibility of the risk of xenogeneic infections by investigating the factors that might have led to the different risk perceptions.

The first analogy is drawn in reference to the emergence of antibiotics, which became a treatment option for a range of bacterial infections in the 1940s⁴¹. Rothblatt notes that the antibiotics were administered with knowledge that improper use could lead to the generation of resistant forms of bacteria, which in turn could form a major public health hazard. Indeed, within a few decades, excessive use of antibiotics has rendered entire new species of antibiotic resistant bacteria, which cause an increasing death toll. The widespread use of antibiotics in both animals and humans has given rise to new human-borne pathogens as well as new antibiotic-resistant zoonoses and constitutes an enduring risk of creating an antibiotic-resistant pandemic. Rothblatt observes that, in contrast to the current attitude towards xenotransplantation, there is no mention of banning or severely restricting the practice. Indeed, the public is willing to accept the risks, as well as the existing harms, in light of the life-saving benefits provided and in the confidence that public health regulations can timely manage the severe harms.

The second analogy is drawn in reference to the development and study of recombinant DNA technology⁴². In that case, the potential scientific and social benefits were not a sufficient justification and the development of the research went hand-in-hand with efforts to control and contain public health hazards. Here too, the potential hazards related to infections from bacteria and viruses. They were taken seriously from the start and some of the world's prime molecular biologists voluntarily implemented a temporary moratorium on the research. In February 1975 stringent requirements were set for the continuation of genetic experimentation. During the Asilomar meeting, the scientific expert invitees were confronted with ultimate uncertainty whether or not cancers or new infectious diseases could result from the splicing of genes and transfer of chromosomes. Consequently, they decided rather to be on the safe side and protective measures were established in accordance with a classification of risk. Experiments that were clearly safe were permitted on the bench top; (possibly) dangerous experiments were restricted to confined areas. Those recommendations have since been adopted by governmental agencies worldwide.

Rothblatt uses the above-mentioned analogies to demonstrate the way forward for xenotransplantation experimentation and clinical practice. The antibiotics analogy highlights certain conditions, which render public health hazards acceptable. The permissibility is a function of the perception of benefits and of the trust that the harm can be effectively controlled once it occurs⁴³. The emergence of recombinant DNA research regulation teaches us that mechanisms can be put in place beforehand to constrain the risks to public health while not necessarily quashing the potentially beneficial research itself⁴⁴. Rothblatt concludes that xenotransplantation can be ethically pursued if similar measures are put in place in advance to detect and restrict related infectious outbreaks globally⁴⁵.

In my view, it is precisely the distinctions between those analogies which provide for extra factors to be weighed when questioning the permissibility of man-made public health hazards.

8.3.2 Foreseeable risk

Arguably, the anticipation of a significant potential for benefit was greater in the advent of antibiotics than in the emergence of recombinant DNA technology. The potency of antibiotics to decrease the high percentages of mortality and complications due to infectious diseases was apparent upon its discovery in 1928: pre-clinical data demonstrated the ability to destroy a common bacterium that was associated with sometimes fatal infections (*Staphylococcus aureus*)⁴⁶. A decade after that discovery, during which diverse technical difficulties were overcome, Howard Florey, Ernst Chain and Norman Heatley were able to show penicillin's capability to provide cures for a wide variety of conditions. By contrast, the advances in therapeutic applications of recombinant DNA technology have been slower and the importance of its potential much more contested.

The recombinant DNA analogy also shows evidence of less public trust that the risks will be manageable at the moment they occur. Instead, it illustrates a focus on preventing the risks beforehand. That may very well be a partial effect of the various time frames. Furthermore, although in both cases the risks were known before the technologies were put to widespread use, the two situations appear distinguishable in terms of the extent to which the risks were predictable and the moral importance of accounting for foreseeable adverse effects.

Rothblatt indicates that the invention of new antibiotics in the 1950s and 1960s convinced society that the emergence of sub-types of antibiotic-resistant bacteria should not pose a great problem⁴⁷. That trust arguably echoed the confidence and public support of medical and other scientific research at a time when laboratory efforts had successfully been mobilized for war⁴⁸. The fruits of those experiments were reaped in the scientific boom years of the 1950s. Asilomar, by contrast, is indicative of a turning point in the ethics of science. It marked the first time that scientists engaged a social contract with society. The moral impermissibility of *knowingly* exposing a population to manufactured risks appears to have increased in significance during the past century. That may relate to the fact that many risks associated with contemporary technology transgress former spatial and temporary limits⁴⁹.

While it appears of paramount importance to take advance account of the risks posed by emerging biotechnologies, there is an important distinction with respect to the extent to which the risks can in fact be foreseen in advance. In the case of antibiotics, the first warnings of the risks arose well after applications on soldiers and only one year prior to widespread clinical use. Antibiotic resistance was marked as a real threat only after two cases of lethal resistant bacterial infections in patients occurred in the 1970s⁵⁰. That was well after the scientists were in the position to exclude that kind of harm beforehand. By contrast, the controversy surrounding recombinant DNA started with evidence of successful insertion of hybrid genes into *E. coli*⁵¹, of which the adverse effects were evident before they occurred. In that case, the scientists were in the position to exclude them from occurring altogether. We believe that that distinction is particularly relevant in understanding the reluctance to accept the public hazard posed by xenotransplantation.

Although the impact of the worst-case harms of xenotransplantation is similar to the impact of the HIV pandemic, much more stringent monitoring and surveillance measures are imposed on the xenograft recipient than on a patient affected by HIV. It has been proposed that the crucial distinction lies in the fact that xenotransplantation will be introduced *purposely* as a clinical experiment, whereas HIV is an 'experiment' of nature⁵². It appears to make a difference to us whether harm was due to natural causes or knowingly brought about by the action of another person. That difference is tied to notions of individual responsibility and human agency⁵³. This is not to say that moral responsibility is attributed to only those effects that were purposely pursued. Rather, the underlying reasoning would seem to be that we are in the position now to annul foreseeable adverse

consequences and thus have a particular moral responsibility to do so. Indeed, the freedom and autonomy of HIV/AIDS subjects is respected to the extent that their acts exclude foreseeable events of virus transmission.

If the permissibility of health hazards posed by emerging (bio)technologies is dependent on the perception that the benefits are both substantive and attainable and on the duty to account for foreseeable risks, there is both good and bad news with regard to the development of xenotransplantation.

8.4 Foreseen risk and benefit

8.4.1 The bad news

Proponents of xenotransplantation have long defended the added values of applying solid organ xenotransplants to resolve the organ shortage problem. An unlimited source of animal grafts could help not only those patients who currently die while on the waiting lists, but also the individuals who are not enlisted on the transplant waiting lists, who are withdrawn from a list prior to their death or who have not accepted human organ donation for ethical or cultural reasons. Moreover, if a sufficient supply of xenografts were readily available, the transplant procedure could be precisely scheduled and preparatory measures could be facilitated⁵⁴. As such, both the graft and the recipient could be thoroughly screened prior to the transplant and the diverse patho-physiological effects of brain death on the organ quality could be avoided.

Nevertheless, xenotransplantation is not a heaven-sent timely solution to the limits of allotransplantation. While attempts to transplant nonhuman animal organs to humans go back to the beginning of last century, xenotransplantation has not been able to live up to its promises to this day⁵⁵. After the failures of early experiments, interest in xenotransplantation was rekindled in the 1960s, motivated by a first wave of human donor shortages (prior to the implementation of the brain death criterion) and by increased knowledge of immunology. During that period, several xenotransplant trials were conducted parallel to some of the first nonrelated human-to-human allotransplants. In terms of the results achieved within both experimental fields at that time, Keith Reemtsma achieved outstanding survival rates of 63 days and 9 months after the

xenotransplantation of nonhuman primate kidneys⁵⁶. Those survival rates remain by far the longest ever achieved in animal-to-human organ transplantation, whereas allotransplantation has since made great strides forward.

It appears unlikely that xenogeneic organs will survive and function in humans for prolonged periods in the near future. Sir Roy Calne, one of the pioneers of the xenotransplantation enterprise, recently pictured that negative outlook. In a commentary entitled 'Xenografting - the future of transplantation, and always will be?', Calne doubts that therapeutic xenografts will be obtained within the next five to ten years⁵⁷. The prospect of using xenotransplantation as the medium to avert the waiting list death toll is currently more based on rhetorical promise than on feasible potential. Indeed, due to the failure to materialize significant progress to the clinic, private industry has increasingly withdrawn or suspended commitment in this area⁵⁸. As set out in Chapter 4, the success of xenotransplantation is obstructed mainly by immunological incompatibilities. Due to the short survival rates obtained to date, the impact of subsequent rejection phases is not yet entirely manifest. The many physiological and biochemical incompatibilities between swine and humans form yet another source of factors that stand in the way of effective and successful use of xenogeneic organs.

Currently, most hope and effort is dedicated to various cellular xenotransplants and extracorporeal perfusion therapies. The transplantation of animal-derived cells is also very promising in terms of treating a wide variety of diseases, among which: diabetes, liver failure, neurodegenerative disease, anaemia, spinal cord injuries, haemophilia, amyotrophic lateral sclerosis, AIDS, hypocalcaemia, hypercholesterolemia, lysosomal storage disease and dwarfism⁵⁹. Nevertheless, many of the cellular therapies differ in terms of urgency and life-sustaining benefit when compared to the need for whole organ replacement. Furthermore, the results of most cellular xenotransplants have thus far not provided compelling indications of progress in graft survival and clinical utility. As noted in Chapter 4, a review of the clinical experience with both extracorporeal pig liver perfusion and bioartificial devices containing pig hepatocytes do not demonstrate a significant benefit for hepatic assist in acute liver failure. The most imminent contribution of xenotransplantation to the clinic is likely to lie in the transplantation of porcine islets of Langerhans. That could provide an alternative to injections of human or porcine insulin, which are ineffective in fully restoring proper glucose homeostasis. Islet cell xenotransplantation may eliminate the need for daily insulin injections and obtain better glucose control. It could thereby avoid or retard development of the various ills and co-

morbidity related to deficient treatment of chronic diabetes. Islet cells from cadaveric sources have been shown to provide at least 1-year insulin-independence in patients with very unstable diabetes ($n=7$)⁶⁰. Two recent reports of more than 6 months of insulin independence in pig-to-monkey transplants provided promising indications of the feasibility of using islets from porcine sources too^{61,62}. As also mentioned in Chapter 4, a recent report of a islet xenotransplant trial in humans suggests that combining porcine islet cells with Sertoli cells and encasing them in a semi-permeable encapsulation device is a promising means to eliminate the immune barrier to cell xenotransplants⁶³.

Although the latter study is encouraging, the fact that xenotransplantation is overall still “very much in its infancy”⁶⁴ ultimately raises questions why that research should gain priority over other technical alternatives for the allograft shortage. Welsh and Evans indicate a fallacy of claims that portray xenotransplantation as the most realistic and rapid solution for those on the waiting list⁶⁵. In comparison with stem cell cloning, for instance, it has been calculated that xenotransplants will be available for clinical use eight years prior to stem cell technology. Eight years is not necessarily a long interim period for the emergence of a novel technology, particularly if therapeutic xenotransplantation is still a long time coming. It is likely that there will be a long lead time between clinical trials and the commercial availability of significant numbers of transplantable genetically modified organs. In light of this, the authors guessed that it would take many years before xenotransplantation can alleviate the waiting lists death toll considerably. In effect, given the high costs and difficulties of breeding appropriate source animals, the question is raised whether xenotransplantation will *ever* make a significant impact on the waiting lists. Moreover, even if the technology of stem cell cloning will take much longer to develop than what is assessed here, it appears to offer a range of advantages over the use of xenotransplantation. At least theoretically, it may avoid the problem of acute immunological rejection altogether, as the prospect is raised that use can be made of the recipient’s own genetic material to generate replacement tissue. Moreover, provided the stem cells are not exposed to living animal-derived material, clinical use of this alternative does not involve a public health hazard.

8.4.2 The good news

In questioning the attainability of xenotransplant benefits, we must also take note of the progress that has been made in the understanding of the level of infectious risk during the

past decade. Indeed, we currently seem relatively well equipped to identify and define the infectious potential of most known porcine pathogens⁶⁶.

Broad exclusion lists have been generated which provide guidance to breeding out organisms particular to the source animal species, organisms that commonly cause infection in transplant recipients and organisms that have a high inclination for recombination. Those lists also facilitate the screening and studying of those organisms and the development of possible infection-suppressive measures. Various potential human pathogens can now be identified in advance, including porcine circovirus types 1 and 2, porcine reproductive and respiratory syndrome virus, porcine encephalomyocarditis virus, hepatitis E-like virus, pseudorabies virus, parvovirus and polyomaviruses of swine⁶⁷. None of these have been shown to cause disease in humans. Recent research suggests that porcine cytomegalovirus, which has been shown to cause severe disease even in immunosuppressed host pigs⁶⁸, can be screened and excluded from herds of swine by early weaning of newborns⁶⁹. Conversely, failed attempts to wean out porcine lymphotropic virus⁷⁰ and the recent identification of hepatitis E virus⁷¹ subject those viruses to further risk defining.

Significant progress has also been made in identifying and excluding the infection or recombination potential of PERV. Archived samples from past recipients of porcine insulin and clotting factors, temporary skin grafts, islet and neural cell xenotransplants, and extracorporeal porcine liver or spleen support have not shown any transmission of PERV or other porcine virus in patients treated with pig tissues thus far^{72,73,74,75,76,77}. Nor is there a clear relation between PERV production and illness in pigs, although PERV-C was originally cloned from a malignant lymphoma cell line⁷⁸. Some authors have expressed concern that the promising results merely reflect the small numbers of patients studied so far, their brief exposure to the porcine grafts, the poor graft survival and an exclusive focus on known PERV strains during follow-up. Although the large-scale follow-up study of 160 patients after transplantation or exposure to pig tissue⁷⁹ is generally viewed as the most compelling demonstration of absence of PERV transmission, Collignon and Purdy drew attention to the more negative outcomes of the study⁸⁰. PERV was in effect detected in the blood of 30 patients. In 23 patients, pig cells were still detected up to 8.5 years after exposure. The authors suggest that at least the first two of four crucial conditions in terms of the potential for secondary infection have been fulfilled: the virus (or its genome) was present in the animal's cells or tissue and remained viable in people after transmission of the virus. Furthermore, studies have recently established the presence of natural immunity

against PERV in human serum, showing that human serum with anti-Gal antibody can inhibit human cell infectivity of PERV *in vitro* and *in vivo*⁸¹. That implies that the use of ‘knockout’ pigs that lack the anti-Gal antibody would entail additional risks. Notwithstanding this, significant knowledge has been gained on PERV infectivity. Previous findings had already suggested that only PERV-A and -B can infect human and pig cells *in vitro*, while the third subgroup, PERV-C, only infects porcine cells⁸². The other PERV families are unlikely to encode infectious virus owing to disruptions in open-reading frames. Certain inbred lines of miniature swine appear to be incapable of producing replication-competent PERV⁸³, and progress in the science of PERV infection of human cells raises the possibility that the relevant PERV could be genetically engineered out of a source animal herd⁸⁴. Moreover, evidence suggests that PERV is susceptible to currently available antiviral agents⁸⁵. More worrisome are indications suggesting that, while PERV-C does not infect human cells, it is involved in extra harmful human-tropic PERV recombinants⁸⁶. A recombinant isolate, PERV-A 14/220, has been shown to infect human cells with a significantly higher titer than previous PERV-A and -B families. Studies of its genome suggest that it is an A/C recombinant PERV and that therefore replication-competent PERV-C should best be excluded from the source animal’s genome. Breeds of miniature swine have been identified which do not possess replication-competent PERV-C⁸⁷.

Alongside the growing potency to recognize and exclude infection risks, a significant distinction must be made with regard to the different types of porcine grafts⁸⁸. The infection risk is directly related to the degree of recipient immunosuppression and the nature and intensity of the epidemiological exposure of the recipient. Cell-based xenotransplantation products imply a significantly smaller risk of virus transmission than xenotransplants of vascularized organs (although at this stage, it could be maintained that vascularized xenogeneic organ grafts pose the least public health threat due to the limited survival rates of the recipients⁸⁹). Cells can also be best screened for a spectrum of infectious agents in advance⁹⁰. Moreover, xenogeneic cell transplant barriers to immunology, such as the above mentioned encapsulation techniques, may control viral transmission as well.

Finally, it should not be left unsaid that immunosuppressed allograft recipients too bear a significant, well-documented virus risk, often with an accelerated course of accidentally-transmitted infection (for instance, transmission of HIV-1 has been shown to manifest AIDS within six months⁹¹). Over the past two years, six organ transplant recipients were

reported to have died after graft-mediated infection of lymphocytic choriomeningitis virus, a zoonosis transmitted by rodents⁹². Use of xenografts may be advantageous in this respect if resistant to human pathogens such as HIV, HTLV, hepatitis and herpes viruses. Moreover, if a ready source of xenografts allows scheduling the transplants at the time of greatest clinical need, exposure to pathogens related to lengthy hospitalizations of donor and recipient will be reduced⁹³.

8.5 Implications of revised risk: an optimistic note

Although so far not conclusive, in the following paragraphs we wish to interpret the development of findings related to the virus risk in an optimistic note (one which we have not accounted for in the previous chapter). We will consider the possibility that all foreseeable factors that contribute to the risks of a xenogeneic epidemic, can be excluded via current pre-clinical methods of porcine infectious agent detection and exclusion.

8.5.1 Theoretical risk

While the advanced xenogeneic virus research suggests that the probability of harm is less great than once feared, it does nothing to change concerns regarding the nature of the risk. Various screening methods may eventually exclude all pathogens identifiable in pre-clinical models. Caesarian section and suitable containment of the source animals may even help to exclude the unknown⁹⁴. Nonetheless, none of those approaches guarantee that the theoretical possibility of latent, asymptomatic infection by unknown or recombined exogenous and endogenous agents is eliminated. Indeed, undetectable organisms constitute the greatest concern of all, particularly if they can remain in a latent state within the source animal and recipient for indefinite time. In contrast to viruses that induce acute symptomatic viral infections, latent viruses can potentially spread easily between immunocompetent individuals and manifest long after the initial recipient is released from hospital containment practices.

In questioning the permissibility of risky technologies, the moral duty to account for foreseeable adverse effects is left undoubted. That moral duty explains why less stringent control measures are required to preclude risks from ‘natural’ causes, such as AIDS, in comparison with risks from man-made causes, such as xenotransplantation and

recombinant DNA research. Nevertheless, a focus on optimal risk assessment to cover all theoretical consequences provokes the reproach that ‘one cannot prove something that is not there’. Granted that sufficient pre-clinical detection and exclusion of known viruses and mutations in the source animals may one day be feasible, it would be asking too much of those involved in developing a new technology to guarantee the exclusion of *all* risks. Indeed, in comparison with the rationale that underlies our attitude towards the emergence of other theoretical epidemics/pandemics, it is questionable why the xenotransplantation enterprise should be answerable to risks of introducing a novel epidemic or pandemic beyond the degree to which such risks are constituted by predictable factors.

8.5.2 Natural and man-made pandemics

If we were able to reduce the infectious risks related to xenotransplantation to a merely theoretical risk - one in which all predicable effects have been eliminated - it would be ambiguous whether we should persist in treating xenotransplantation as a ‘special case’ and in subjecting it to severe advance public health protection measures. The only thing that would distinguish the risk of xenogeneic virus contamination from the contamination of a nature-borne virus, would be the fact that the xenogeneic virus resulted from human agency. It is not clear why the fact that the harm results from a man-made technology demands for unequal consideration over nature-derived harm. The argument works both as a means to put the ‘unique harm’ of this man-made technology into perspective and as a reminder of our duty to take ‘natural’ health hazards at least as seriously.

First, the distinction between a natural epidemic/pandemic and a man-made one is not a relevant factor for those in the medical community concerned with treating the effects⁹⁵. Also, that distinction is not always clear-cut. In the emergence of certain pandemics of so-called natural origin, humans have also played an inflicting role. Notions of moral responsibility and blame do not apply in such cases, because the effects were unforeseen. Explanations for the spread of Human Immunodeficiency Virus (HIV) are illustrative in that respect. There is compelling evidence that HIV (-2 and some types of -1) is a derivative of Simian Immunodeficiency Virus (SIV) and was transferred to the human population from sooty mangabeys and chimpanzees in Africa⁹⁶. Most probably, SIV was transmitted to humans through blood contact during hunting and field dressing of the animals. Nevertheless, secondary viral transmission may not result in an epidemic unless certain

conditions are met. A sporadic HIV infection in a small, remote African village could have been restricted to the infected person and his or her sexual partner(s) and close contacts. Their resulting deaths would have prevented further contaminations. The rapid spread of the virus among larger proportions of society was interdependent upon certain demographic and social conditions. They are said to include the massive emigration from rural areas for employment opportunities, the separation of family units that resulted from that migration and the increased rate of extramarital relations and sexual promiscuity⁹⁷. An alternative description of the origin of the HIV pandemic, argued for by Louis Pascal in 1991⁹⁸ and recently brought to our attention again⁹⁹, ascribes an even greater function to human agency. According to this theory, SIV was transmitted to humans through the world's first mass polio vaccination campaign in central Africa during the late 1950s. Those polio vaccines were cultured on monkey kidneys, which would have allowed for the transfer of SIV. Whether or not that is the better theory, it is generally agreed that those involved in the African polio vaccination campaign cannot be held responsible for AIDS¹⁰⁰. The reason why no one is to blame is that SIVs had not been discovered at the time and the contamination, when it occurred, was inadvertent.

Most of the contemporary naturally-caused infections, such as the annual variants of type A and B influenza, also arise at least in part due to human agency. The ways we alter the ecology of the world in which we live - through technology, industry, agriculture, international travel, etc - and the interdependence of humans and animals are particularly conducive to the emergence of new zoonotic pathogens^{101,102}. In a cautious approach to xenotransplantation, the claim is made that:

Of course, animals have transmitted viruses and other infectious pathogens to humans ever since we learnt to hunt or husband them, yet we continue to meet nasty surprises.¹⁰³

This does not necessarily serve to demonstrate the unacceptability of the *theoretical* risk of xenogeneic infections that are beyond our control beforehand. Rather, it shows us the urgency to deal with the persistent manifestation of new epidemics, regardless of their cause.

Against that, it may be argued that xenotransplantation would not be accessible for all those in need of it and could still increase the health burden of those who are arguably the worst-off in terms of health care. The worst-off are indeed the developing world, which bears more than 90 per cent of the global disease burden¹⁰⁴ and has neither the financial

means nor the infrastructure to provide large-scale basic health care, let alone expensive technologies to alleviate organ shortage. Nevertheless, an unjust distribution of the health burdens would not be alleviated significantly by avoiding the risks of xenogeneic infections altogether. A much greater balance of health benefits over burdens would be achieved if theoretical xenogeneic infections were regarded as one of the many global pandemic threats that face all of us today - and in the future - and that call for rapid response. In thinking of those who are amongst the most disadvantaged in terms of basic health care, a strong emphasis should be placed on an estimated 34 to 46 million people affected with HIV/AIDS¹⁰⁵, and on many other infections, such as malaria¹⁰⁶, which are among the leading causes of death worldwide. AIDS is particularly illustrative of the gross discrepancies between the industrialized and the developing world in terms of infectious health burdens¹⁰⁷. Sub-Saharan Africa accounts for 75 per cent of the global AIDS-related mortality¹⁰⁸. If we are in fact worried about the unjust distribution of health harms worldwide, then those patient populations ought to be the subject of further investigation and intense efforts to constrain the risks and manage the effects. In light of the fact that zoonoses currently constitute one of the major threats to human health, the systems for studying, controlling and preventing zoonotic diseases on a global basis must be further expanded. Others have voiced the opinion that the looming threat of bioterrorism is an extra motivation to invest more in a biodefence plan^{109,110}.

The optimistic account of the permissibility of a xenogeneic virus risk is nonetheless dependent on whether or not we can exclude predictable factors of the infectious risk beforehand. Even if that is feasible, the onus for those wishing to implement the various xenotransplantation procedures in the clinic lies in demonstrating greater proof of the benefits they promise to provide. That is of importance in terms of outweighing the remaining risks of physical harm to the future recipients. Progress in the effectiveness of xenotransplantation is also needed to justify the continuous financial investments in research, which are currently being provided mostly by governments rather than by the private industry.

8.6 Conclusion

In attempts to balance the benefits and harms potentially involved in xenotransplantation, the benefits for the prospective patients have been subordinated to the potential risks of unleashing a xenogeneic pandemic. National and international restrictions on clinical

research and trials have been set in place in order to exclude the risks for the public, but they may not prove to be fully effective for both practical and ethical reasons. The question we have attempted to answer here is whether the requirement of those stringent public health measures is inevitable. We argued that, even though the harm principle dictates that harm-doing is unacceptable when it is also other-regarding, the impermissibility of harming public health is not a moral absolute. In particular, an assessment of the acceptability is dependent on whether the promised benefits are attainable and perceived as such by the public. Furthermore, there is a particular responsibility to take account of those risk factors that have a predictable, foreseeable effect. It can be argued that accountability for a pandemic that results from an *unforeseen* effect of xenotransplantation should not necessarily be attributed to those involved in the development and use of the technology alone. The permissibility of harm-doing is then rendered an issue of medical ethics, in which a weighing of harms against the benefits of the procedure for the patient is of paramount importance.

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PART FIVE

HUMAN/ANIMAL INTERCHANGEABILITY:

CONSEQUENCES FOR HUMAN AND PERSONAL IDENTITY

9 Pig tales and human chimeras: socio-ethical issues related to xenograft recipient self-perception

Adapted from: Ravelingien A. Pig tales and human chimeras: socio-ethical issues related to xenograft recipient self-perception. Submitted.

Abstract

Several surveys have identified a fear among the public that use of porcine grafts for transplantation in humans will affect the recipient's appearance, behaviour, and/or personality. This chapter aims to investigate both the direct and indirect effects that xenotransplantation may have on the recipients' sense of self. We demonstrate that direct effects on personal identity are unlikely. If nonetheless effects should appear, they would be very similar to those in the case of allotransplantation. What rather seems to be at stake is the possibility that the *conception* of self will be indirectly affected. In the field of allotransplantation, there is evidence that certain perseverant cultural concepts interfere with the view that the human grafts are purely neutral, mechanical replacements of one's body parts. In questioning whether the fact that the donor is an animal will worsen the danger for identity conflicts, we trace and compare various cultural categorizations that constitute a potential conflict between 'self' and 'other'.

Twelve voices were shouting in anger, and they were all alike. No question, now, what had happened to the faces of the pigs. The creatures outside looked from pig to man, and from man to pig, and from pig to man again; but already it was impossible to say which was which.¹

9.1 Introduction

Due to the shortage of human grafts for transplantation, pigs are considered a possible alternative source of cellular and solid organ graft replacements. One of the main limitations of that approach - xenotransplantation - is the short survival of the grafts when transplanted into humans due to severe immunological rejection. In addition to that, the use of animal grafts for human transplantation must also be accepted on a cultural level. Most importantly in this respect, society must legitimize the risk of virus transfer from the animal source to the human recipient, a risk that may affect the community at large. In a very different way, the recipient and the people that surround him, must also accept the socio-psychological implications of the emerging biotechnology.

Various studies have established that the level of acceptance of xenotransplantation is most dependent on the seriousness of the prospective patient's health condition and on the effectiveness of the xenotransplant to provide a safe cure^{2,3}. When xenotransplantation is perceived as a means to save lives, even religious considerations do not override the significance of that goal^{4,5}. Although close contact with the pig is prohibited in Islam and Orthodox Judaism, both religious ideologies are accepting of the use of porcine organs until a more suitable alternative is found⁶. After a careful examination of the acceptability of xenotransplantation, the Vatican Pontifical Academy for Life also pronounced no fundamental objections⁷. Nonetheless, the Academy did detail several preliminary issues which must be attended to, among which the condition that the xenotransplant must preserve the identity of the person who receives it. That specific requirement has also been brought up with regard to transplantation of human grafts (allotransplantation) in an official address of Pius XII (Address to the Italian Association of Corneal Donors, Clinical Ophthalmologists and Legal Medicine, 14 May 1956) and John Paul II (Address to the Eighteenth International Congress of the Transplant Society, 29 August 2000, n. 7)⁸, and in the Islamic Code of Medical Ethics⁹.

Surveys demonstrate that the public shares the concern that pig graft replacements will have adverse effects on the recipients' identity. In a study of the attitudes of 100 transplant patients towards the use of xenotransplantation, 24 respondents believed a xenograft might influence them in appearance, personality, sexual habits or in their attitude towards eating meat¹⁰. In a German inquiry conducted by Schlitt *et al.*, 15 per cent of the 1,049 transplant patient respondents indicated a fear for personality change¹¹. In a survey questioning Parkinson's patients on their attitudes to xenotransplantation, Lundin *et al.* found that the patients were uncertain whether the transplant could transmit the source animal's identity or other nonmaterial characteristics and whether the animal would take up residence in them¹². Lundin also conducted qualitative interview studies with patients who underwent a xenotransplant in the 1990's to treat either diabetes or Parkinson's disease. She found that, in contrast to the Parkinson's patients, all diabetic patients indicated a need to know of the whereabouts of the porcine cells. One of the respondents compared the porcine cells to "small piglets," "tiny pig cells that I have no control over and that can pump something animal-like into my body."¹³ The fear of being influenced by the characteristics of the donor is also indicated in a survey conducted by Sanner to investigate the general public's beliefs about receiving transplants with varying origins (n=69)¹⁴. Sanner lists various citations that illustrate respondents' worries regarding the possibility of becoming more 'piggish' after receiving a porcine graft: "I would perhaps look more piggish with a pig's kidney;" "Would I become half a pig, if I got an organ from a pig?" "What if I would start grunting?" "At least 5 per cent of me would become animal."

There is little literature on the origin of those concerns and on the ways in which identity alterations may indeed materialize as a concrete effect of xenotransplantation. This chapter aims to investigate both the direct and indirect effects that xenotransplantation may potentially have on the recipients' sense of self. We will demonstrate that direct effects on personal identity are unlikely. If nonetheless effects should appear, they would be very similar to those in the case of allotransplantation. What seems to be at stake is rather the possibility that the *conception* of self will be indirectly affected. That phenomenon has been well identified in the field of allotransplantation and is said to involve culturally inspired assumptions regarding the embodied self. Granted that cultural notions of body and self play a preconscious role in the psychological adjustment to transplants of human grafts, we suggest that they may intensify difficulties to objectify transplanted grafts derived from animals.

9.2 In search of the pig's tale: explanations for donor-mediated identity transformations

The anxieties of the respondents expressed above reflect the fear that xenotransplantation may affect the recipient in such a way that he or she is no longer the same person. Essentially, that relates to the potential impact the procedure will have on the recipient's personal identity. The concept of 'personal identity', in general terms, pertains to the whole of conscious and persistent thoughts expressed by 'I', the experience of being a unique person with particular beliefs, interests, preferences and experiences. That psychological continuity is what John Locke referred to in his definition of a person:

(...) a thinking intelligent being, that has reason and reflection, and can consider itself as itself, the same thinking thing, in different times and places.¹⁵

The importance of maintaining personal identity throughout time is clear enough. It is the precondition of a notion of responsibility for past actions and practices of praise and blame¹⁶. That reveals why it is so crucial from a moral and religious viewpoint. Preservation of personal identity is also the *condition sine qua non* for planning future goals in accordance with the present views, interests, preferences and characteristics that make up one's self. Ultimately, within this context, a radical change of self due to a xenotransplantation would imply that the health-enhancing results are no longer of benefit to the prior person the transplant aimed to benefit, because that particular person has ceased to exist.

When reflecting upon the nature of personal identity, however, we must acknowledge that our identity is in fact in a *constant* state of transformation. All people are, in the course of time, as a result of aging and of accumulative experiences, liable to changes of a gradual nature. Those changes do not seem to negate the impression of a continuing identity. Even drastic changes in body and character do not necessarily threaten the feeling that the resulting person is still you. Sometimes even the contrary is the case. For instance, patients who have undergone curative medicine treatments may feel that the changes in their body constitute a reinstatement of their 'normal', healthy personality prior to disease¹⁷. Dorothy Bernstein gives the example of a 14-year old boy who, one year after a human kidney transplant, noted that:

I had thirteen years of needles and feeling lousy before my transplant. Now I can go ahead and be myself.¹⁸

The question that arises, then, is what changes could cause alterations to someone's personal identity after a xenotransplantation, to such a degree that the recipient no longer experiences him- or herself as the same person he or she was before the transplantation?

9.2.1 Personal identity: it is all in your head

As a possible response to that question, the Vatican Pontifical Academy for Life states the following:

(...) the encephalon and the gonads, are indissolubly linked with the personal identity of the subject because of their specific function, independently of their symbolic implications. Therefore one must conclude that (...) the transplantation of these last can never be morally legitimate, because of the inevitable objective consequences that they would produce in the recipient or in his descendants (...)¹⁹

The Vatican statement hereby precludes both xenotransplants of gonads and of the encephalon. The issue of gonad xenotransplantation is the least compelling concern in terms of direct effects on the identity of the recipients. Although theoretically the recipient could produce descendants with nonhuman DNA - and as such would violate the biblical order that species should multiply after their kind - that procedure does not carry a risk of altering the recipient's personal identity. It rather implies the possibility that the genetic identity between recipient and descendent will differ significantly. Moreover, while the intermixing of human and nonhuman sperm and ova and the creation of a human/nonhuman animal hybrid zygote has been attempted in the past²⁰, the development of a viable embryo through transplantation of cross-species gonads is implausible.

Whole brain xenotransplantation

Through vague reference to transplants of the 'encephalon' in the quoted statement, the representatives of the Catholic moral position appear to preclude xenotransplantations that involve the *entire* brain. That that would indeed result in the insertion of a new personal identity, or at the very least, the termination of the recipient's personal identity, is evident from the fact that the brain is the controlling mechanism for psychological continuity. Indeed, the brain is the *only* part of the body that can have a pertinent role in

the preservation of the self. John Locke first illustrated that in a thought experiment of ‘The Prince and the Cobbler’²¹, which has since inspired many other versions that make the same case. In its original form, a prince and a cobbler wake up one day in the other person’s body. The cobbler’s body carries the consciousness of the prince’s past life, and vice versa. We are asked to resolve whether the cobbler’s body is still accountable for his crimes. Reflection on the outcome of such an example forces us to acknowledge that it is not. In mind-swapping scenarios, the person has simply changed bodies, finding him- or herself wherever his or her mental life now resides²². In light of that, it is obvious why xenotransplantation involving the entire brain should be precluded. The transfer of a viable animal brain into a human body would imply that the animal is still alive and has merely switched bodies. Whole brain transplants would not be a new brain for the recipient, but rather a whole new head and body for the donor²³.

Brain tissue xenotransplantation

It is unclear whether the Vatican statement would also preclude transplants that involve the transfer of partial brain tissue or neurons. That procedure stands closer to the therapeutic goals of current xenotransplantation research. Pig embryonic neural tissue has been transplanted in a few small-scale trials as part of an ongoing effort to provide alternatives for scarce human neural grafts. Such xenotransplants have primarily involved patients with Parkinson’s disease^{24,25,26}, but patients with Huntington’s disease²⁷, focal epilepsy and stroke^{28,29,30} have also been experimentally treated.

To our knowledge, there are few³¹ detailed objections to neural xenotransplants on the basis of feared-for effects on the recipients’ personal identity. The advent of neural allotransplantation, by contrast, did elicit considerable debate regarding the extent to which certain neural replacements threaten the integrity of the recipients’ identity. In the establishment of the Swedish codes for neural transplantation research, there was more focus on that issue than on the fact that the neurons would be obtained from an ethically provocative source: aborted human fetuses³². The relevance of the concern relates to the potentially long-lasting and direct effects of cellular implants on the host brain. Transplanted grafts can produce more drastic and irreversible effects than pharmacological therapies generally do³³.

In debates on the risk of personal identity alterations after neural allotransplantation, the most radical position makes no distinction between the replacement of only a few neurons

and the replacement of the whole brain³⁴. The opponents indicate that the insertion of however small an amount of foreign material into a recipient's brain will result in the insertion of a new personality. Underlying such a view is a strong sense of personal identity, which is based on the presumption that the brain is not only carrier but also *substrate* of personal identity. Accordingly, personal identity preservation is strictly dependent on brain identity preservation; any change of the structural composition of the brain must necessarily entail an alteration of personal identity. From a neurophysiologic perspective, the condition of spatio-temporal continuity of the brain is refuted by evidence that the alterations in some regions of the brain seem to be particularly dangerous with regard to lasting effects on the patient's personality, whereas other regions do not interfere with personal identity. For instance, psychosurgery has shown that disruption of psychological continuity can result from the removal of particular brain areas such as the frontal lobe and the limbic system³⁵.

From an alternative point of view, the acceptability of neural transplantation would perhaps depend on restrictions of the proportion of engrafted neurons. It could be argued that, whereas the insertion of a small amount of neurons would not interfere with personal identity, there is a critical threshold level beyond which the increased amount of cells constitutes a new or altered identity. To the extent that that position, too, rests on the structural composition of the self, it is implausible. The self is not structured in special 'personality cells'; it is rather the consequence of a set of trillions of co-active neurons that form a specific configuration of interconnected modules. Since changes in the brain structure are not necessarily accompanied by changes in character traits, the risk of personal identity alterations relates to the risk of interfering with the major connections between those modules. In other words, a change of personality and behaviour would require a 'rewiring' of that functionally organized network. Hence, if an implant does not alter the functional organization of the recipient's brain and only restores the degenerated brain structure, there is no influence on the graft recipient's mental or physical characteristics, and therefore, one can assume, no influence on his or her identity³⁶.

It is not impossible that transplants of entire brain regions between closely related, functionally and morphologically similar animals will affect crucial functional areas in the host brain and result in a transfer of functional behaviour. An experiment conducted by Balaban *et al.* indicated that possibility³⁷. The group transplanted brain tissue from developing quails into the brains of foetal-stage chickens. The tissue contained the neural circuitry that is connected with auditory perception. Once born, the chickens exhibited the

vocal trills that are unique to quails. Notwithstanding that, it has long been accepted that transplants of dissociated cells do not interfere with the functional organization of the host brain³⁸. Even transplants of small pieces of integrated tissue are often functionally regulated by several cortical areas³⁹. It is thus generally accepted that the risks of personal identity alteration are negligible when the neural transplants consist of small tissue or dissociated cell grafts only. The risks of damaging personal identity are even reversed if neural replacements can restore the brain functions of the degenerated neurons and thereby alleviate pathological changes in character traits and loss of personal identity⁴⁰. Granted that there are no substantial differences between porcine and human neurons - a presumption that is supported by the anatomical and functional compatibility of porcine grafts with the human host^{41,42} - there appears to be no reason why neural xenotransplantation would constitute more of a threat to personal identity than neural allotransplantation.

9.2.2 Mad pig disease

There is one plausible distinction between xeno- and allotransplantation in that regard. Xenotransplantation bears a risk of transmitting animal viruses that would not be transferred to humans under 'normal' circumstances. Theoretically, a xenogeneic virus could be transferred along with the xenograft into the recipient and replicate in neural tissue, causing an infection that affects the brain. Indeed, neurological disease is one of the most serious complications of virus infection. Several infections in the brain are known to cause changes in the patient's personality and behaviour and may even cause severe intellectual impairment and death. Particularly illustrative in this regard is the emergence of Creutzfeldt-Jakob disease, which is strongly linked with exposure to the Bovine Spongiform Encephalopathy (BSE) agent that affects cattle⁴³. Nonetheless, so far, no reports exist that demonstrate the emergence of neurological disease as a result of a xenotransplant. It has even been argued that the circumstances under which the xenograft source animals are bred and maintained provide a unique opportunity to generate an extensive microbiological specification of the grafts prior to transplantation⁴⁴. Such assays will allow the exclusion of most of the known (exogenous) infectious agents from the source animal⁴⁵. Moreover, xenogenic cells can be encapsulated in a semi-permeable membrane with a controlled pore size, which may modulate the risk that a virus passes through⁴⁶. As such, the risks of obtaining a personality-affecting virus are not outstanding in comparison with neural allotransplantation. Allotransplantation also carries small, but

non-negligible risks for neurological disease through transfer of human viruses such as herpes virus and cytomegalovirus⁴⁷.

9.3 Recipient self-perception and the embodied self

9.3.1 Biographical cells

Above, we relied on common arguments to refute the pertinent role of the body in the preservation of the self. We indicated that sustained personal identity does not require that the identity of the whole body is unaltered; it merely requires continuity in memory, character and personality. Given that those mental functions are functionally organized in the brain, we can conclude that even if one's entire body is replaced by porcine parts, but the brain is left intact, the self continues to exist. Moreover, given that the self does not require that the structure of the brain is unaltered, only those xenotransplants that affect the functional integration of the self bear a risk of altering the self.

Nevertheless, the survey responses quoted above do not specifically apply to the risks of neural transplantation. Worries are also, perhaps even more so, evoked in questioning the effects of receiving a solid organ xenotransplant. The belief that the 'donor' can influence one's identity is a not uncommon phenomenon within standard allotransplantation practices. Various observations have been made of patients who received a human organ (other than the brain) and feel that the transplant has a transformative effect on his or her behaviour, habits, interests and tastes^{48,49,50}. Extraordinary examples of such cases include a Ku Klux Klan member who became an advocate for black rights after receiving a black cadaveric donor's kidney⁵¹. In another case, a lady recipient of a heart transplant suddenly felt more masculine and acquired a taste for beer and green peppers. Allegedly, it was later discovered that the personality of the donor mirrored those specific changes⁵². Another bizarre example is that of a young heart recipient whose recurrent nightmares are said to have provided her with accurate descriptions of the man who murdered the donor of her heart⁵³. The peculiarity of those stories lies in the fact that recipients of cadaveric human organs are generally withheld of any personal descriptions of the donor, aside of perhaps the most general information such as age and gender.

In response to those puzzling data, theories are put forward claiming that the spirit, memory or, ultimately, *mind* of the donor can linger in the donated graft. ‘Spiritual mediums’ declare that because of the often *abrupt* death of the donors, his or her spirit may not have yet realized that the body it was retrieved from is dead⁵⁴. Alternative suggestions from a more scientific standpoint have cropped up as well. The ‘gut feeling’ concept has been explained by reference to the brain-independent actions of the hundred million nerve cells in and around our guts⁵⁵. By analogy, the idea is suggested that there are various pathways between cells throughout our body and brain which can allow for the transfer of *biographical* information regarding our personalities, tastes and histories. Andrew Armour, for instance, introduced the concept of ‘neurocardiology’ and suggested that the heart consists of its own nervous system with an independent communicative quality⁵⁶.

Surely, there is a sense in which the mind is inseparable from the body. One does not need to regress to the Cartesian arguments and claim that the self is not any kind of body, to contest that the whole body is the vehicle of the self. In an obvious sense, the mental aspects, which constitute our psychological continuity, are the result of physical processes. In another sense, the self *has* a body with which it constantly interacts. There are a range of information systems throughout the body that supply information about its state and performance. The interaction involves both conscious and unconscious registration and feedback of somatosensory perceptions and sensations from the entire body. There can be severe distortions on the level of registration and feedback. Patients with a phantom limb, for instance, will continue to experience the missing limb and attempt to integrate it in their movements. Conversely, an existent body part can be blocked from awareness, which can cause an individual to no longer experience it as belonging to him- or herself (asomatognosias)⁵⁷. Against that, however, there is no proof for the claim that information obtained from body parts could be in any sense biographical, which would be the result of a complex conscious awareness (indeed, other explanations have been provided for the alleged identity transfer⁵⁸). The body parts are *objects*, not *subjects* of sensory and perceptual awareness.

9.3.2 The embodied self

Although there is no factual change in the mental states that constitute the persistent identity of the patient, the stories of donor-mediated identity transformation and the

alternative theories to explain them provide evidence of cultural resistance towards transplantation in one way or another. Clearly, the views dismiss the concept that identity has a merely neural locus. There appears to be a perseverant cultural endorsement of traditional (animistic) assumptions of bodily integrity with the self, which obstructs the view that grafts are purely neutral, mechanical replacements of one's body parts⁵⁹. Evidence of the reluctance to accept brain-centred personhood can be found, for instance, in the continuous public ambivalence towards the concept of brain death⁶⁰.

Various authors have emphasized the importance of embodiment in relation to symbolic conceptions of corporeality and identity^{61,62}. Even for those who acknowledge the body as an object rather than a subject of awareness, embodiment is a significant aspect of how one perceives his or her self and body on a conceptual, partially socio-culturally determined level. Due to the intense relation between the experience of our identity and the experience of our own body, body parts may be viewed as an extension of one's self-concept. Indeed, for some, a concept of the self may largely converge with a concept of the body. As such, the convergence of body and self-concept conflicts with the transplant image of the body as composed of bits and pieces that are interchangeable with spare parts from other sources. In light of this, the question has been raised whether xenotransplantation:

(...) takes us yet one more step away from an *integrated theory of personal identity* - seeing ourselves as unique, indivisible human beings - and further along the line of a *modular theory of human identity* - that we are simply a series of interchangeable parts, and these parts can now include animal parts - and a "gene machine" view of human life?⁶³

An integrated theory of personality renders the recipient of a transplant a compound of 'self' and 'other'. That perception may even amount to a sense of conflict, in which the transplanted material is experienced as a rival object of the self. This has been described as the cultural equivalent of the immune-based physiological processes of rejection:

(...) it is important not to underestimate the cultural force behind the idea that self and cell are not entirely separable, that it is not only the brain in which the "I" resides. After all, as is made clear by even a cursory view of the process of rejection, the intuition of bodily integrity has a solid biological foundation.⁶⁴

Joralemon establishes a "non-negotiable and indelible" immunological boundary between self and non-self in reference to the fact that "the body never accommodates to the presence of foreign tissue"⁶⁵. Similarly, an emotional barrier may constitute a level of

psychological rejection of the foreign tissue. Reluctance to psychologically accept the transplanted organ as a part of the own identity is well known within the allotransplantation field. Medical-anthropological data have long confirmed that the fact of having a part of another person's body placed within the own body, causes an internal disturbance and a sense of 'otherness' for many transplant recipients, despite intense counselling to neutralize those feelings. Post-transplant patients commonly experience problems that may lead to adverse effects on perceived physical appearance, self-esteem, and sexual functioning^{66,67,68,69}. Ultimately, the attribution of anthropomorphic characteristics to a transplanted graft can be seen as part of the coping process to resolve the conflict between 'self' and 'other'⁷⁰.

Whether the integration of a transplanted graft will worsen when the source of the organ graft is another *species* is impossible to foretell from the data we have today. There are some indications that xenotransplantation may be more favourable in that respect. For instance, pig heart valves and insulin have been used for many years and have not seemed to raise any objections⁷¹.

Also, it has been observed that struggles to objectify an organ worsen when the transplanted graft itself is of symbolic and iconic import. Particularly relevant in this respect is the dominant symbolic meaning of the heart. In their survey of heart transplant recipients (n=35), Inspector *et al.* show that nearly half of the respondents expressed a notion of having possibly acquired at least some of the personality characters of the donor along with the heart itself⁷². That was the case regardless of an advanced knowledge of the anatomy and physiology of the heart. Renée Fox and Judith Swazey bring to our attention a story of a widow whose desire to feel her husband's presence drew her to visit the man who received his donated heart:

The kidneys, liver and lungs, she decided, were hidden deep away in the bodies of those who had received them. How could she possibly get to hem? The corneas just didn't seem right. She didn't think she could relate to a cornea. That left the heart. A heart can be listened to. A heart can be felt.⁷³

In comparison, organs obtained from animals will perhaps have a neutral denotation. Conversely, we can imagine that the fact that the pig is typically viewed as filthy and demeaning will erode the symbolic meaning of certain organs for some people and will be experienced as offensive.

To some, the more a transplanted graft poses a physical threat, the greater the psychological difficulties to integrate the 'other' into the embodied self will be⁷⁴. In support of that, for instance, a follow-up study of children who had undergone kidney transplantation found that a child rejected the concept of owning a new kidney when experiencing postoperative abdominal pain⁷⁵. In a survey of ten adolescent recipients of porcine islet cells and their parents, Téran-Escadón *et al.* found that there was only one patient who - briefly - considered the possibility of acquiring porcine features. The authors referred to the level of anticipated physical rejection to explain the favourable results. They noted that the encapsulation technique used to implant the cells consists in embracing the porcine cells by device walls. That functions as an immunological, and perhaps also psychological barrier between the nonhuman animal and the human material⁷⁶. The fact that cellular xenotransplants pose less of a physical encroachment on the human body is also one of the reasons why the general public has shown to prefer the use of animal cells to the use of whole organs⁷⁷.

Unsurprisingly, problems of psychological adjustment to a transplant have also been related to the ways in which the transplant compromises the appearance of the recipient. Obviously, visually confronting forms of transplantation will worsen the distress. Note that two years after receiving the first hand transplant, the recipient asked for an amputation because he felt mentally detached from it⁷⁸. Surely xenotransplants will not involve transplants of eminently expressive and visually confronting parts of the body such as limbs. Nonetheless, xenotransplantations of larger tissues and organs will most likely require high levels of immunosuppressive drugs, which may also affect outward appearance. Adverse effects on appearance, such as the occurrence of Cushingoid syndrome (which causes puffiness of the face as a result of excess of cortisol hormone) after renal transplantation, have been shown to affect the self-concept and make it unstable, particularly in adolescent girls⁷⁹.

Another aspect that may contribute to difficulties in objectifying a transplant graft could be the extent to which the recipient can identify with the donor. The origin of the organs is not insignificant for the individuals that have incorporated them. It has been observed that an altered sense of self is a common reaction when the transplant is known to be derived from a donor with a different gender, age or ethnicity^{80,81}. In that respect, xenotransplant recipients may be even more aware that their transplant identity is a compound of self and other. Furthermore, the conceptual dichotomy between embodied self and other is perhaps only one of the culturally defined dividing lines of the self that is

being challenged by xenotransplantation. Possibly, symbolic or ideological categorizations of the animal and the human world will intensify the reluctance to incorporate an animal graft.

9.3.3 Cultural category transgression

Human-to-human transplantation: flesh out of place

A particularly interesting argument, which favours xenotransplantation over allotransplantation with regard to potential problems of self-perception, has been made in drawing an analogy between allotransplantation and cannibalism. When asked whether they would accept either a xenotransplant or an allotransplant, some respondents expressed the idea that they would not accept an allotransplantation because it would feel as though they were cannibalistic^{82,83}.

That argument is puzzling in several respects. Typically, the ‘yuck factor’ is explained as a response to the novelty and unfamiliarity of *emerging* technologies. However, while xenotransplantation is still in an experimental phase, allotransplantation has evolved into an accepted and widely applied form of medicine over the past 50 years. It is also worthwhile to ask the question why the current life-saving use of human graft transfer should bear the same connotation of the ancient taboo related to the historical consumption of human flesh. Conceivably, the cannibalism-allotransplant analogy can be explained as the perception of ‘matter out of place’.

Mary Douglas’ cultural anthropological work on premodern ideas of danger and impurity⁸⁴ is widely cited in attempts to explain cultural aspects of moral reluctance towards modern technologies. Douglas suggests that societies must classify their world in order to organize, interpret and control it. Those classificatory systems are of symbolic importance, allowing people to classify their social life into what is acceptable and what is not. Societies are likely to view things as dangerous, impure or taboo, when those things concern anomalous practices that do not fit neatly within the cherished existent conceptual categories. Hence, one could argue, whereas the grafting of animal tissue fits within the culturally accepted concept of meat consumption, human-to-human graft transplantation is not in accordance with any such preliminary judging category. The human flesh is not in its right place in the symbolic order.

Animal-to-human transplantation: 'beast' out of place

If the argument against allotransplantation is put forward that to have another's human organ in one's body would be 'matter out of place' - perhaps in general, there will be stronger ambivalence about the use of animal grafts. Arguably, there are more conceptual categories at stake here. Most importantly, xenotransplantation involves the transgression of the concept of being 'fully human'⁸⁵ and, figuratively speaking, the creation of 'monsters'.

We borrow the monster metaphor from Martijntje Smits, who employs it to depict emerging technologies that inspire both fear and fascination in the public⁸⁶. That ambivalence is explained as the result of the ways in which those technologies produce problematic *mixtures* of established cultural categories. A monster, in her interpretation, is a particularly confusing situation that relates to more than 'matter out of place'. It arises when a new phenomenon not only challenges the symbolic place it is normally accorded, but also when it simultaneously fits into two conceptual categories that would normally mutually exclude one another. An obvious example of a 'problematic mixture' is the monster of Frankenstein, the horror prototype par excellence. Victor Frankenstein's creation is viewed as a monster because of its particular merge of at least two culturally perceived dichotomies: organism/machine and living/cadaveric body parts. In comparison with allotransplantation, xenotransplantation may be viewed as particularly 'monstrous' in that it simultaneously converges life/death, organism/machine and, in addition, human/animal boundaries.

Although the use of certain animal products, such as porcine heart valves, for medical purposes is widely accepted, the xenotransplants we conceive of here are more problematic mixtures of culturally perceived dichotomies. Xenotransplantation by definition implies that the transplanted grafts are still physiologically active. As such, xenografts are both cadaveric body parts from dead source animals and *living* tissue, potentially capable of repairing and regenerating some of the vital functions of a living human body.

There are various ways as to why the use of such grafts for transplantation could be regarded as trans-bordering cultural categorizations of the animal and human world. Certain aspects of our Western culture reveal symbolic or ideological constraints to the use

of pig organs and tissues. For instance, as Smits points out⁸⁷, the prospective xenograft source animal has always been regarded as a ‘monster’ in traditional Hebrew culture. In the Old Hebrew taxonomy of animals, quadruped animals were considered to be either ruminants with cloven hoofs, or non-ruminants without cloven hoofs. The pig, non-ruminant but with cloven hoofs, transgresses both orders. Moreover, whereas East Asian religions deny such a clear demarcation, the Judeo-Christian tradition explicitly considers the line that divides humans from nonhuman animals - as part of the many binary divisions described in Genesis - as sacred⁸⁸. Throughout Western history, the ‘beast out of place’ metaphor has been portrayed in art, literature and architecture to serve as symbol of fascination, deviance, unnaturalness and even terror. The fact that the xenograft recipient is, literally, a *cross-species chimera* - an organism that in part consists of genetically distinct cells from different species - evokes the connotation of the term ‘Chimerae’ as it first occurred in Homer’s ‘Illias’:

(...) a thing of immortal make, not human, lion-fronted and snake behind, a goat in the middle, and snorting out the breath of the terrible flame of bright fire.⁸⁹

In mythology, the fire-spouting monster terrorized the Lycians of Asia Minor before being slain by the young, unwitting Bellerophon⁹⁰. The ‘composite beast’ is also a regular figure in medieval literature, with its fascination for wondrous, exotic hybrid races, such as the dog-headed Cynocephali or the horse-bodied Onocentaurs⁹¹. The 16th-century Monster of Ravenna is a cluster of disjointed pieces of various animals that serve as symbols for pride, lack of ‘good works’, rapaciousness, unspiritual nature and sodomy⁹². Even in the more contemporary science fiction scenery, chimeras are rarely as attractive, good-hearted and clever as the ‘normal’ specimens of nature⁹³.

Just as animal composites have more often than not been represented as problematic, the reverse case - that problematic situations have often been conveyed as a blurring of that which is animal and that which is distinctly human - also applies. For instance, symbolic talk of the ‘beast in man’ is in reference to human’s raw, uncivilized and uncontrollable nature. Pathological conditions in humans have been associated with bestial characteristics and named accordingly. Illustrative in this respect are the ‘lobster-hand’ condition, the ‘lion-head’ condition and the legendary example of the man nicknamed ‘The Elephant Man’, who suffered from deformities so severe to suggest animal shapes and to which he owed being treated like a beast rather than a human.

9.4 Discussion: implications for xenotransplant recipients

The concern that xenotransplantation will cause concrete identity alterations in the recipient is restricted to those forms of neural xenografting that potentially affect the brain functions that are responsible for psychological continuity. In that respect, the safety profile of neural tissue xenografting is essentially comparable to that of allogeneic tissue⁹⁴. Granted that xenotransplantation does not pose a great risk of infectious brain disease, there is no need to distinguish between the two in recommendations as to how to proceed. As part of the informed consent requirement prior to any risky therapy, it would seem essential that in both cases, the prospective recipients are informed on the possible adverse effects of neurosurgery and brain implants on personal identity.

The psychological struggle to incorporate the transplant as part of how one perceives his or her self, is a potentially indirect effect of the xenotransplantation. We have represented several interpretations of how xenografting may interfere with symbolic, socio-culturally defined experiences of the self. Most importantly, in accordance with known coping processes after having received an allotransplant, a xenotransplant recipient may find it difficult to integrate the foreign graft into the notion of an embodied, indivisible self. Additionally, the recipient may feel ambivalent about the cultural boundary between that which is animal and that which is human. Other factors still may contribute to difficulties to adjust to the xenotransplant psychologically. The mere fact that xenotransplantation is an extraordinary, 'state of the art' approach to augment health, can contribute to the recipient's awareness of being 'not normal' and 'at risk'. Being attributed an 'extraordinary' survival status has been reported to bear additional connotations of disability and 'otherness' within the context of allotransplantation⁹⁵. Furthermore, psychological distress may be worsened by reactions from others. Conceivably, even besides the cultural notions that it brings to mind, xenotransplantation may stigmatize recipients due to the risk of animal-to-human infections. For some authors, the risks to the recipient's self-image are, from the viewpoint of the individual involved, a strong ethical objection to xenotransplantation⁹⁶.

If xenotransplantation evolves into a successful procedure, it is, as mentioned earlier, unlikely that any psychological ambivalence will seriously affect the potential candidate's decision to participate if his or her health gravely depends on it. It can also be expected that this type of fear would not represent a relevant problem for most patients after the transplant, particularly if it involves the transfer of cells rather than solid organs. If it does

occur, moreover, it will probably be of a temporary nature. Indeed, having conducted various surveys on the attitudes towards xenotransplantation, Susanne Lundin suggests that cultural underpinnings of xenotransplant recipients' identity concerns will gradually fade away. She refers to the example of 17th century vaccinations with cowpox virus, which also elicited the fear that the patients would develop animal characteristics. That concern nevertheless steadily transformed into perceptions of a safe and self-evident treatment⁹⁷.

While that is likely to be the case, any possible initial concerns are nonetheless valid insofar as they will contribute to additional emotional distress for the patient. In the Secretary's Advisory Committee on Xenotransplantation (SAXC) Guidelines on Informed Consent in Clinical Research Involving Xenotransplantation, it is suggested that the informed consent process should involve a team of individuals with the expertise to educate the potential recipient about various areas, among which the potential social, economic and *psychological* consequences of the xenotransplant to the subject and his family⁹⁸. While we endorse this recommendation, we believe that such attention should also be provided during the treatment and psychological follow-up of prospective patients. The relevance of being attentive to these concerns lies in the fact that psychosocial issues may prevent the recipients from regaining quality of life. They may also prevent the recipients from achieving long-term health enhancement. It is conceivable that difficulties to adjust psychologically to a transplant may compromise the willingness to comply with immunosuppressive regimens. Emotional problems such as depression and anxiety⁹⁹ and a negative body image¹⁰⁰ have been reported to elevate the risk of lower medication compliance in some patient subpopulations. It would therefore seem crucial that adverse factors of a patient's psychological and emotional wellbeing are timely recognized and managed.

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10 On the moral status of humanized chimeras and the concept of human dignity

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Abstract

In this chapter, we will discuss an issue that is related to the broader interpretation of xenotransplantation (as interspecies transplantation) to include the creation of human-to-animal chimeras. Recent advances in the technology of creating chimeras have aroused controversy in policy debates. The centre of controversy is the fear that a substantial contribution of human cells or genes in crucial areas of the animal's body may at some point render the animal more humanlike than any other animals we know today. Authors who have commented on or contributed to policy debates specify that chimeras that would be too humanlike would have an altered moral status and threaten our notion of 'human dignity'. That setting offers a productive opportunity to test the notion of human dignity and to emphasize some of its weaknesses as an ethical tool. Limiting chimerism experiments on the basis of whether or not it undermines or challenges human dignity, implies a clear demarcation of those characteristics that are typically, and importantly, human. Evidence of our evolutionary ties with and behavioural similarities to other animals seems to annul all attempts to define the uniquely human properties to which human dignity may be attributed. Hence, it has been suggested that the particular moral status associated with humans cannot be explained for beyond an intuitive basis. In what follows, we will argue that the difficulties inherent in the notion of human dignity, do not lie in the impossibility to acquire a list of properties that are unique to humans, but rather in the difficulty to demonstrate the moral relevance of those properties and particularly the relevance of their being human. We offer an alternative interpretation of the concept of dignity, which is not necessarily related to being human.

Were I (who to my cost already am)
One of those strange, prodigious creatures, man
A spirit free to choose for my own share
What case of flesh and blood I pleased to wear,
I'd be a dog, a monkey or a bear,
Or anything but that vain animal
Who is so proud of being rational.¹

10.1 Introduction

Our cultural history shows a great fascination for imaginary creatures that transgress supposed species boundaries. The mythologies, legends and arts of ancient and modern cultures are abundant with imagery of fantasy beasts, a great number of which contain features of both nonhuman animals (hereafter 'animals') and humans. Examples range from the animal-headed gods of ancient Egypt to Greek mythological depictions of the Centaur, Triton, Sirens, satyr, sphinx and medieval legends of werewolves and vampires. The meanings and values attached to those fantastic creatures are as diverse as the distinctive cultures from which they are generated and the audiences they are aimed at. More often than not, however, particularly within the Western traditions, human/animal composites represent evil or at least misconduct (Spiderman and Batman excluded). Indeed, the devil has commonly been depicted as a composite of human and snake, dragon or goat features. According to medieval legends, the unfortunate human that was possessed by the devil would transform into a werewolf. Present-day science fiction narratives of human/animal combinations often repeat the logic that intermixing human and animal characteristics is sinister. With H.G. Well's 'The Island of Dr. Moreau' as a classic prototype, some of the most horrifying science fiction tales today sketch the gruesome effects of suppressing or altering an animal's nature by raising it to a level more proximate to that of humans. Recent works draw upon the topicality of genetic engineering and cloning to recount the emergence of aggressive, rebellious freaks or oppressed, suffering subhumans^{2,3}. Their dreadful destiny is depicted as the backlash to the attempt to reconcile bestial instinct with human intelligence or as the side effect of purposely enhancing a species for refined slave labour. Note that, according to recent press coverage, the creation of such a subhuman species has been actively and intently

pursued in the past under Jozef Stalin. Secret documents are said to show that Ilya Ivanov experimented (in vain) on human-ape crossovers in the mid-1920s in an attempt to create an invincible breed of Red-Army warriors and new labour forces⁴.

We now have the potential to transgress the biological boundaries between humans and other animals in ways that were unthinkable during the Stalin reign. Recent advances in technology have brought fears concerning the creation of enhanced animals to the forefront of current policy debates. The centre of controversy is the anticipation that the blending of animal and human material will be so profound that the resulting chimeras will verge on the concept of what it means to be 'human'. It is that concern, and in particular the difficulty of analyzing what is included in the notion of 'humanness', that we address in this chapter.

10.2 The moral worth of an ambiguous entity: a 'mind-bending' controversy

The chimeras we refer to here are, in the strictest sense, entities characterized by the side-by-side presence of both human and animal cells in embryonic, foetal or adult individuals. Often broader interpretations are used interchangeably in the literature to include genetic forms of commingling: organisms that consist of an exogenous, human gene (transgenics or genetic chimeras), organisms made out of cross-species gametes (genetic hybrids) or out of somatic cell nuclear transfers between humans and animals (nucleocytoplasmic hybrids). Such chimeras prove to be of great utility for many research and prospective therapeutic purposes. One medical therapy, currently under development, involves the creation of 'animal-to-human chimeras' through the transplantation of animal-derived grafts into human bodies (i.e. xenotransplantation). The use of cells, tissues and organs from animal sources is considered to be a possible alternative for the transplantation of those human grafts, of which there is a growing shortage. Most chimeras, however, are 'human-to-animal chimeras' which are created by adding human cells or genes to an animal's genome or developing body. As we saw, that approach is applied to create source animals with more compatible grafts for transplantation in humans. Most chimeras, however, are developed as research models to enhance our understanding of the aetiology and progression of human disease and to test new treatments. Although the best animal models for humans are humans, animals with close proximity to human physiology or animals which - through artificial means - exhibit

significant human cell and tissue populations, provide the next best study environment. The use of chimeras as research tools initiated with the creation of mice with fully human immune systems for the study of HIV in 1988⁵. Today, they are a particularly promising means to further explore the ways in which stem cells develop, contribute, integrate and react to the host environment and various chemical influences before stem cell technology can be of established clinical use for human patients. That field of research has generated a range of remarkable experiments. Scientists have injected human embryonic stem cells labelled with a fluorescent protein into mouse blastocysts, which later developed into embryos and were carried to term by foster mice. The fluorescence in the offspring's tissues allowed the researchers to study cell line contributions to the various tissues, organs and the nervous system⁶. Human foetal neural stem cells have been transplanted in rat and mouse models for research, which may potentially be the basis for effective stem-cell based treatments of various neurodegenerative diseases^{7,8}. In a study of the distribution and integration of human neural stem cells, mice have been created whose brains are almost 1 per cent human⁹. The hope exists that eventually the chimeric mice brains will consist of 100 per cent human neurons¹⁰. Human neural stem cells have also been injected into the brains of vervet monkeys and Old-World monkey foetuses^{11,12}.

Although a mouse brain consisting of exclusively human neurons is not a feasible prospect in the near future, that sort of research has elicited a sense of moral unease. The controversy is conveyed by popular press coverage titles such as 'Scientists put a bit of man into a mouse,' 'Human-brained monkeys,' and 'The laws of man and beast'^{13,14,15}. Much of the concern relates to the (theoretical) possibility that a substantial contribution of human cells or genes in crucial areas of the animal's body would render the animal more humanlike than any other animals we know today. Particularly disquieting in that respect is the potential to commingle human and animal genetic material at pre-fertilization and pre-natal stages and to insert substantial amounts of human neural (stem) cells into developing animal brains whose body plans have not yet been fully completed.

Past experiments of cross-species neural tissue transplantation have demonstrated the feasibility of transferring so-called species-specific behaviour. We referred to the experiment by Balaban *et al.* in the previous chapter. The concern about the potential to create more humanlike animals is also supported in reference to reports of successful transfer of human nuclei into enucleated cow and rabbit oocytes^{16,17}. While the resulting nucleocytoplasmic hybrids would consist of an entirely human nuclear genome, the nonhuman mitochondria could indeed leave some traces of animal DNA¹⁸. The successful

fertilization of non-enucleated frog eggs with human nuclei even evokes the theoretical possibility of creating embryos with equal contribution of both sets of chromosomes¹⁹.

On a policy level, the question that arises is whether, and on what basis, certain chimerism experiments should be constrained. In the US the current prohibition of experiments that involve the implantation of human embryonic stem cells into nonhuman primate blastocysts or vice versa²⁰, emerged as a response to the US President's Council on Bioethics' request for clear lines concerning the mixing of gametes or early blastomeres is concerned. The Council motivated its request stating that "(...) we do not wish to have to judge the humanity or moral worth of such an ambiguous hybrid entity."²¹ Authors who have commented on or contributed to policy debates specify that chimeras that would be so humanlike that they would have an altered moral status and threaten our notion of 'human dignity', are at the forefront of the ethical controversy^{22,23}. If the chimeras were to share the characteristics that are otherwise unique and important to human beings, human dignity would be undermined and the chimeras would deserve the same respect as humans.

10.3 Begging the question of human dignity

The notion of 'human dignity' is essentially a deontological one, indicative of a standard by which all people should be treated. It is based on the idea that there is something unique about the human race in comparison with the rest of the world that entitles all humans to an inherent moral worth and exclusive protection. The ethical mandate to respect the dignity of every human being forms the foundation of universal human rights and has played a role in the constitutional legislation of different nations. The concept is also increasingly applied within the context of bioethics. Nevertheless, it is a problematic tool to resolve bioethical questions of the sort we describe here.

The controversy concerning chimeras requires that we draw a line for those organisms that are so human that they undermine or transfer the dignity that should be assigned to humans. That suggests that we have a precise demarcation of those aspects of being human to which dignity is attributed. Nonetheless, human dignity is among the least clearly defined notions²⁴. The use of that concept in the policy behind this²⁵ and other emerging scientific advances²⁶ has been criticized to the extent that it fails to indicate or sufficiently support what exactly is so unique about the human race that all of its

members, and at the same time no others, merit a special, profound moral worth. The criticism applies even to the legislative context. Legally, a violation of human dignity occurs when a human being, or a part of a human being closely associated to the whole human being, is treated as a commodity²⁷. That rationale was the original reason why Stuart Newman's human/animal chimera patent application - a strategic attempt to force the US Patent and Trademark Office to decide on the theoretical creation of chimeras containing up to fifty per cent human DNA²⁸ - was denounced. The PTO ruled that such chimeras would imply a violation of the Thirteenth Amendment, which forbids slavery and the ownership of human beings. It was not at all clear where the boundaries for humanness were to be drawn and how human an animal-human mixture must be for human legislation to apply. The argumentation for the denial of the patent has since shifted towards another principle, the beneficial-utility doctrine, according to which inventions are excluded when harmful for society's wellbeing, good policy or good morals²⁹.

In a position paper on the ethics of transplanting human stem cells into nonhuman embryos, Karpowicz, Cohen and van der Kooy attempt to resolve the problem by referring to the fact that humans possess certain *functional and emergent psychological capacities* more than any other animals³⁰. They suggest that the acceptability of chimerism experiments is dependent on whether the functional and psychological characteristics associated with human brains develop in the chimeric experimental subject. In a different paper, the three authors define a working concept for human 'dignity' that relates to a rough list of capacities³¹. Included in that list are the capacities for reasoning, choosing freely, acting for moral reasons and on the basis of self-chosen purposes. Also included in the cluster are capacities to engage in sophisticated forms of communication and the presence of certain emotions, language, social relations and world-views.

Intuitively, we all grasp that the cluster of capacities they list cannot be excluded from what it means to be human rather than any other animal. Nevertheless, that attempt to give content to the notion of dignity does not provide support of those characteristics beyond a purely intuitive basis. The cluster of properties deemed distinctively and importantly human, is presented as self-evident and lacks argumentation as to why it is superior to another filling-in and as to what degree those characteristics are lacking in other animals. As a consequence, it seems that we would be well advised to look again at the notion of human dignity, and particularly at the criteria of 'humanness' on which it is based, before we can deploy it as a threshold marker for chimerism experiments.

10.4 The downfall of human uniqueness

Before we can determine how a specific biotechnology may threaten the human moral status, we need to know what functional and emergent psychological capacities that status is attributed to. Over two thousand years of philosophical thought on human nature have not provided general agreement on a list of characteristics or capacities that distinguish human beings from other animals³².

Ever since early Greek philosophy, the changeability and variability of the world motivated a quest for stability and a hidden, unchanging essence that constituted the true nature of living things. Whether it be in reference to the true and universal Forms, an inherent natural telos, or the general belief that God created each species independently, species boundaries existed and humans could be distinguished from all other animals. Indeed, the precise humanesque essence which was identified from the outset, not only distinguished humans from other animals, it also elevated humans and brought them closer to the level of the divine, as the genesis narratives of the creation of humans in the image of God demonstrates. For centuries, the Great Chain of Being viewed humans as having a fixed place between the earthly and the heavenly creatures. Humans were connected to animals in terms of instinct and desire, but our capacity to transgress that animal nature through rationality marked the line in terms of what makes us ‘humans’ and what allows our unique position in nature to be the one closest to God³³. The human capacity for reason and understanding was both carrier and vehicle of our human nature, be it in terms of human flourishing or capacity for knowledge of the divine. Reason was as much a moral as an intellectual faculty, granting us the power to evaluate natural events and allowing us to freely and rationally control the motives from which we act and achieve our ends. Starting from the notion that other animals are ruled by ‘instinct’, whereas we humans have surpassed our instincts and replaced them with ‘reason’, ‘intelligence’ or ‘learning’, more specific distinctions were put forward as the main ‘essence’ of *Homo sapiens*. Among the most prominent historically sanctified qualities are our tool-making, social, emotional, lingual, political, cultural, economical and aesthetical capacities. Our capacities for reasoning have also given rise to attributing to humans, and to humans only, an ability for abstract thought, which in turn is the basis of science, religion and conceptions of mortality.

One of the obstacles in distinguishing humans from animals in terms of instinct and reason was the lack of a natural foundation for that dichotomy. In 1698, for instance, Edward

Tyson dissected a male chimpanzee -the first recorded great ape to be brought to England- and found more anatomical and functional similarities than differences between the chimpanzee and humans, in particular in terms of the large brain. In publishing his observations, Tyson was compelled to explain the difference between humans and the so-called Pygmie³⁴ in terms of an immaterial principle or rational soul in humans, independent of a physical organ:

...if all depended on the *Organ*, not only our *Pygmie*, but other *Brutes* likewise, would be too near akin to us. ... in truth *Man* is part a *Brute*, part an *Angel*; and it is that *Link* in the *Creation*, that joyns them both together.³⁵

The sharp distinction between humans and other animals was not left unchallenged, even predating Darwinian theory. David Hume, for instance, denied that reason was a uniquely human capacity and that it provided us with anything more than a means to achieve the natural desires we share with other animals³⁶. And whereas Tyson felt challenged by the anatomical similarities discovered between chimpanzees and humans, three quarters of a century later, Lord Monboddo published the view that ‘Ourang Outangs’ were related to humans and capable of acquiring language³⁷. The theory of evolution nonetheless gave the starting shot for fully undercutting attempts to ascribe a fixed essence or set of traits unique to our species and common to all members.

The theory of natural and sexual selection allows for elucidating the commonality of features across species boundaries. All species overlap to some extent as the result of their common descent and of the adaptive problems that led evolution without any definite direction and without any sharp break amongst species. Rather than the fixed creation of distinguished species, species evolved over evolutionary time through the gradual variation between individual organisms and in particular through the natural selection of those traits that provided the better solution for recurring environmental demands posed by their particular ecological niche. If the traits were able to solve those adaptive problems, they may have - directly or indirectly - promoted a better prospect of survival and possibilities for reproduction, whether it be in the effect of the organism’s own offspring or the offspring of kin³⁸. By the spreading of genes, the traits that formed the better response to the adaptive problems were passed on to later generations. Over evolutionary time, the selection of favourable traits accumulated and gradually developed an integrated, functional response to the adaptive problem.

The origin of human capacities for reason and related faculties, such as the psychological characteristics listed by Karpowicz *et al.*, are as much as any traits of a given species the result of this process. They are the product of circuits that - systematically, and over many generations - have become incorporated into our neural design for their ability to cause adaptive behaviour. Hence, to the extent that various species share the phylogenesis and social and ecological adaptive problems with our hominid hunter-gatherers, they can be expected to share some of these traits. In this respect, the chains amongst animals, including humans, appear interweaved rather than linearly sequenced³⁹.

Indeed, a grasp from studies of the behaviour and cognition of animals, most significantly of great apes, reveals the ways in which animals border on or overlap with the so-called typical human characteristics. Many of the complex cognitive, emotional and psychological capacities which underlie the concept of *Homo politicus* or *Homo economicus* - such as the capacities to reason, abstract, generalize, generate symbolic representations, engage in sophisticated social bonds and to have a concept of self - have to a certain extent been recognized in other animals, most notably in the great apes. Observations of chimps in the wild and in captivity have long described how chimps solve problems, use and modify tools to retrieve food in their surroundings^{40,41}. Recently, the first documented use of tools among gorillas in the wild showed how they fathom the depth of a swamp with sticks and stumps⁴². Ape language experiments strongly suggest that great apes can acquire symbolic communication and basic aspects of grammar, although without syntax⁴³. Great apes and dolphins recognize a paint spot on their face in their own mirror reflection^{44,45}, which some authors suggest is indicative of a level of self-awareness. Frans de Waal has provided many indications of basic human economic tendencies in animals, particularly in capacities for resolution, reciprocity, and political cooperation^{46,47}. Chimpanzees use various media of exchange, such as grooming, sex, support in fights, food and babysitting. They act in a way that suggests implied reciprocity, not only for positive, but also for negative acts. Empirical data even suggest that the value attributed to the currencies is dependent on their availability. De Waal and many others also argue that great apes are cultural beings, when culture is defined as the social rather than genetic transmission of behaviour⁴⁸. Some degree of moral behaviour has also been suggested by indications of reconciliation, empathy, and acts based on the concept of fairness⁴⁹. While already non-experimentally observed by Darwin and described in his 'The Descent of Man', the first experimental indications of a capacity for empathy in monkeys were derived in the 1960s. Rhesus monkeys refused to pull a chain that delivers food for themselves if by doing so a companion receives a shock. One monkey persevered in not pulling the chain for 12 days

after witnessing another monkey receiving a shock⁵⁰. Capuchin monkeys have been reported to respond negatively to previously acceptable awards when another monkey arbitrarily gets a better reward⁵¹. That suggests a relative notion of fairness in terms of the distribution of gains and in choosing between various alternatives to a given outcome. Furthermore, examples have been provided of nonhuman volitional or motivational behaviour. Great apes not only seem to have desires and preferences which they want to fulfil but also the mental abilities to satisfy them, which suggests that they have some degree of autonomy⁵².

Our evolutionary ties with other animals and the evidence of a gradual behavioural continuum seem to annul all attempts to set out those uniquely human traits to which human dignity may be attributed. The lack of distinctive, fixed boundaries draws Robert and Baylis, in an explorative paper on the biology of species identity and the morality of crossing species boundaries, to reconcile with the idea that:

We all know a human when we see one, but, really, that is all that is known about our identity as a species.⁵³

As the authors indicate, since evolution points to variability and not to essential sameness, attempts to identify what is uniquely human cannot even appeal to a complete sequence of the human genome. Our genome is for the greater part shared by a huge variety of apparently distantly related creatures and, for the remaining part, it lacks a genetic essence that is identifiable as absolutely common to all *Homo sapiens*⁵⁴. Moreover, given the differing intellectual abilities, moral capacities, communication skills, and so on, among humans, we are a far cry from identifying a specific functional or psychological property on which to base human nature.

10.5 Defining humans as a set of mental and emotional adaptations

If we do not know how to define a human, then we can scarcely resolve the question whether or not a future chimera expresses a distinctively human trait. Nor can we even begin to discuss whether it thereby challenges our notion of human dignity. However, while it is one thing to establish that a distinctive essence shared by all and only the members of a given species is lacking, it is quite another thing to assume that we cannot describe our human nature or even draw some unique differences with the nature of other species. Although Darwin is known for his argument that humans share many of the same

mental properties with nonhuman animals, natural selection can just as well serve as a research tool to establish distinctive human features.

As noted above, the only kind of traits we can expect any given species to express are those that proved *functional* in solving specific adaptive problems. The entire anatomical, physiological, cognitive, psychological and emotional architecture of humans - or any other species for that matter - is thus the result of a set of adaptations that were gradually 'engineered' to respond to the specific adaptive problems of our hunter-gatherer ancestors. Were we able to construct the entire list of adaptations with insight of their functional history, we would have a very rich notion of what typifies our species. An understanding of the neural adaptations that have given rise to our cognitive, psychological and emotional architecture would also allow for a specification of those complex mental characteristics that constitute what most people will relate to human nature.

Of course, not all aspects of our architecture are clearly adaptations in the technical sense of the word⁵⁵. Particularly very specific and 'higher' cognitive functions did not develop directly for adaptive reasons, but nevertheless built on adaptations that came about for different purposes. Natural selection did not select any mental devices to create Non-Euclidean geometry, for instance, given that it does not seem to reflect a relevant adaptive problem for our evolutionary ancestors. Indeed, in a famous debate between Darwin and Wallace about the origin of our capacities for mathematics and science⁵⁶, Wallace argued that human cognition must be an exception to the theory of evolution; our ability to engage in higher reasoning must be the result of divine creation. However, in the development of skills to create geometry, we utilize the same adaptations that proved useful in the prehistory, such as the capacities for abstraction, orientation, and elementary calculations.

Attempts to derive a list of those adaptations that compromise our human nature involve 'reverse engineering' the structure of the human mind and behaviour by working out the adaptive problems that our ancestors needed to solve⁵⁷. Every one of our evolved neural adaptations - which range from our capacity to perceive colour and dimensions to capacities to form social bonds through sophisticated communication and to order our world in abstract categories - allowed us to interact with a particular domain or to resolve a particular difficulty in our environment. By identifying the specific environmental demands that required a specific type of information processing, an adaptationist

perspective can provide testable hypotheses to determine the nature of the traits that accumulated into neural programs and were incorporated into our behaviour.

A full typology of human nature would necessarily consist of characteristics that are shared by other animals. Nevertheless, an adaptationist perspective could also demonstrate some of the characteristics that are uniquely human. The degree to which humans differ from other animals can be drawn from those adaptations that arose in response to the particular adaptive problems *not* shared by the ancestors of other species⁵⁸. The *distinctively 'human' nature* can then be defined as the accumulated set of psychological, cognitive and emotional adaptations that arose in response to adaptive problems that only the ancestors of our species were confronted with.

10.6 Discussion: implications for the concept of dignity

Although research into the origin of evolved human neural modules is relatively new, the tools and means to derive a list of those adaptations that characterize human behaviour, exist and the compilation of such a list is, at least, feasible in the future. The remaining problem for our purposes, then, is not so much how to acquire a list of the traits that typify humans and distinguish them from other animals, but rather how to *use* such a list to define human dignity and to weigh the acceptability of cross-species experiments. It is not clear which of the characteristics that typify humans merit the superior dignity and respect and why that may be so. The philosophical-anthropological questions of 'what is human nature?' and 'what is distinctively human about it?' now shift to the question what the moral relevance of those human characteristics is.

Various problems arise when attempting to attribute privileged moral status to factual descriptions of (characteristics of) human nature. Philosophical criticism regarding the is-ought problem will hold on to the idea that there is simply no acceptable basis on which to relate moral status to biology⁵⁹. It is arguable that ethics should not be entirely independent of a biological understanding of the nature of our species. Nonetheless, while an evolutionary psychological approach may to some extent reflect fundamental factual aspects of human nature, the value of that particular nature does not follow directly from such a description.

Before we can weigh the degree to which certain human characteristics merit respect, we need to construct a hierarchy of those characteristics. Any such moral ranking will always be subject to dispute rather than it will be an objective truth. In that sense, the property cluster proposed by Karpowicz *et al.* seems as good a shot as any. The functional and psychological capacities they sum up (capacities for emotions, reasoning, choosing freely, acting for moral reasons and on the basis of self-chosen purposes,...) intuitively evoke higher notions of respect. Those capacities resonate with descriptions of ‘personhood’, the notion that underlies an individual’s unique personal identity and serves as the starting point for the indication of various basic moral principles⁶⁰.

Provided that we can achieve a consensus on how to rank human capacities in terms of moral worth, it will remain difficult to ethically evaluate the permissibility of a chimerism experiment if a human-to-animal chimera happens to express some of those characteristics. The problem lies in the difficulty to achieve a *minimum* basis for human dignity and to demonstrate that the relevant capacities included in such a minimum basis are exclusively human. As demonstrated above, other animals express some of the so-called human capacities in varying degree. As such, it is in no way clear that the minimal conditions for human dignity lie beyond the reach of ‘non-enhanced’ animals. Limiting human dignity to those capacities that are distinctly human, will not resolve the problem. It may be pointed out that whether a certain chimerism experiment does or does not elicit the expression of distinctively ‘human’ capacities is beside the point and errs on speciesist convictions. The dignity is not attributed to the mere fact that a certain trait is typical for humans; it depends on how that trait is ranked according to moral worth.

Many philosophers have argued that the prevailing reasons to distinguish between the treatment of humans and that of animals fail the test of moral relevance. Peter Singer has advocated that the moral category, which is of central importance to assess the respect due to all living creatures, relates to the interests and capacities they have⁶¹. In that respect, and as was argued in Chapter 6, the most minimal criterion of moral relevance lies in a being’s capacity to experience pain and happiness. Jeremy Bentham identified that as the prerequisite to having interests. That ‘minimal’ notion of dignity does not necessarily strip the concept of human dignity to a single, most rudimentary capacity. There is a wide variety of ‘range’ in capacities to suffer and in their moral weight. The moral worth of the capacity to suffer depends on the specific type of suffering, be it merely physical suffering or more advanced forms that require emotional and rational capacities and that are of greater influence on the interests of any given individual. The

acceptability of chimerism experiments would thus depend on the degree to which the experiments cause the animals to suffer and affect their interests.

In conclusion, several implications can be related to the weaknesses that are inherent in ‘human dignity’ and the use of that notion to evaluate the acceptability of chimerism experiments. While it is not *in se* impossible to distinguish between uniquely human characteristics and characteristics shared with other species, no such distinction will be a direct guide for our moral actions. Rather, a typification of what it means to be human or some other type of species will be the starting point to discuss the particular moral relevance of the characteristics and to compare the degree to which various species-typical characterizations overlap. Since we do not have a solid description of species-typical features yet, nor a consensus on the moral ranking of those features, and since we lack insight in the impact of chimerism experiments on the alteration or transfer of potentially morally relevant features, questions regarding the dignity of chimeras and the acceptability of far-reaching experiments remain highly debatable. At the very least, given that there are certain types of capacities (minimally, capacities related to suffering) to which we attribute higher notions of respect, and given that those capacities are not necessarily unique to humans, nor shared by all humans, it makes more sense to speak of ‘capacity dignity’ rather than ‘human dignity’. That approach allows discussing moral worth as a matter of varying degree, rather than an all or nothing state.

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PART SIX

GENERAL DISCUSSION

11 Summary, implications and recommendations

Adapted from:

Ravelingien A. The world is my patient: a discussion of Martine Rothblatt's 'Your life or mine: how geoethics can resolve the conflict between public and private interests in xenotransplantation'. *Xenotransplantation* 2005; 12(2): 88-90.

Ravelingien A, Braeckman J. The patients' perspective: comments on 'Reluctance of French patients with type 1 diabetes to undergo pig pancreatic islet xenotransplantation'. *Xenotransplantation* 2005; 12(3): 173-4.

Ravelingien A, Braeckman J, Mortier F, Mortier E, Kerremans I. Author's reply: a body at will. *Journal of Medical Ethics* 2006; forthcoming.

"The time has come," the Walrus said,
 "To talk of many things:
 Of shoes - and ships - and sealing wax -
 Of cabbages - and kings -
 And why the sea is burning hot -
 And whether pigs have wings."¹

In the introduction of their book on the ethics of allotransplantation, Caplan and Coelho maintain that many dimensions must be considered in order to understand the ethical implications of allotransplantation medicine². Those dimensions unfold in an interplay between complex scientific, sociological, philosophical, political, legal, economic and religious issues. They clearly manifest in an ethics of xenotransplantation as well. The previous chapters portray only some aspects of the 'xeno-phobia' that may arise when assessing the implications of this biotechnology. However, it was our intention to gain insight into the predominant concerns that hinder the development of xenotransplantation. In doing so, we restricted our scope to a debate on several unique harms that xenotransplantation may infer. In this final section, we reflect on the results of that exploration.

11.1 Summary and implications

As set out in the General Introduction, an ethical assessment of xenotransplantation must apply to a plural setting, taking into account the possible harms caused to the source animals, the individual patients and the community at large. In our consideration of what constitutes harm, we opted for a broad approach and delineated the concept minimally as ‘adversely affecting interests’. We have balanced such possible harms against the anticipation that xenotransplantation will offer immense benefits to humans. Xenotransplantation has been recognised as a potentially successful therapy for patients with advanced organ failure who currently have no alternative treatment. It also promises to improve the quality of life of thousands of people with such diverse conditions as degenerative brain disease, epilepsy, chronic intractable pain syndromes, paraplegia due to spinal cord lesions and insulin dependent diabetes.

Those expected benefits prevail over many *a priori* concerns regarding xenotransplantation. As we saw, studies of public acceptance of xenotransplantation indicate that the seriousness of the prospective patients’ health condition and the effectiveness of the xenotransplant to provide a safe cure are the primary considerations. The same will likely be the case for the targeted patient population. Although various socio-cultural factors may contribute to difficulties to adjust to a xenotransplant psychologically, it is unlikely that any psychological ambivalence will seriously affect the potential candidate’s decision to participate if his or her health gravely depends on it. Religious considerations regarding the interference with nature, or the use of pig grafts as ‘replacement parts’, are also overridden by the potential benefits of improved quality and quantity of life, at least according to studies on the positions of Catholic, Jewish and Islamic authorities. Sykes *et al.* suggest that xenotransplantation may also be an accepted alternative for religions that do not accept cadaveric allotransplantation³. Although Buddhism and Hinduism strongly instruct the protection of animals and the need to maintain the integrity of the human body before death, respectively, both teachings leave room for individual choice⁴.

However, in order for the potential benefits to counterweigh the ways in which xenotransplantation threatens the wellbeing of those involved, a more delicate balancing is in place. In the following, we summarize our account of how such a balance can be secured.

11.1.1 Harm to non-persons

The pigs used as sources for human replacement technology have interests that are of moral relevance in their own right. We have resisted an absolute elevation of humans above other creatures and have maintained that moral worth must be attributed to an entity's capacity to suffer. As such, we have defended a notion of 'capacity dignity' - a hierarchical concept that is based on the level of evolved mental and behavioural capacities relevant to suffering - rather than a notion that would automatically attribute dignity to characteristics that are or appear to be uniquely human. That approach allows us to discuss moral worth as a matter of varying degree, rather than an all or nothing state.

Some of the conditions under which the pigs are born and raised are disrespectful of their 'capacity dignity'. Those conditions aim at enhancing the safety and quality of the prospective grafts prior to clinical use. Although the intrinsic concerns against transgenesis are not essentially relevant in this respect, the potentially harmful physiological effects of this imperfect technology are. Adverse effects on the wellbeing of the pigs are also related to the environment in which they are reared, which subjects them to sensory deprivation and precludes the manifestation of natural behaviour such as rooting and foraging. The animals are also confined to living in small groups. That may deprive them of sufficient social interaction, particularly the weeks before the harvest of the xenografts, during which the animals must be quarantined. In establishing that nonhuman primates can suffer significantly from those 'psychological' harms, it would be wrong to feel reassured that pigs couldn't. Hence, those conditions thwart their interest to experience pleasure and avoid suffering. Furthermore, the very intent for which the pigs are bred necessitates a premature ending of their lives, in other words, a premature termination of their interest to seek pleasure.

This notwithstanding, there are sound arguments that do not undervalue the moral worth of pigs but provide a reasonable trade-off of those harms. The arguments follow the paradigm rule that unequal consideration of interests is morally acceptable on the condition that the interests themselves are unequal. The concrete (psychological) suffering during upbringing forms a sound basis for resisting xenotransplantation, because pigs have as much an interest to avoid momentary suffering, as do humans. Nonetheless, in so far as

humans are persons and pigs are non-persons, humans have a stronger interest in *continued* life because they have a conscious interest in actively pursuing *future* pleasure seeking, whereas pigs do not. In other words, the harm to the pigs in terms of premature death can be outweighed by the fact that premature death of persons would constitute an even greater harm. That argument is dependent on the condition that the pigs are killed humanely. It seems reasonable to accept that the 'greater good' may also, to some extent, outweigh the harm done to pigs during upbringing, particularly if everything is done to reduce unnecessary suffering. Precisely where we draw the line in resolving the conflict between the welfare of persons and non-persons will remain a matter of dispute. Whether the interests of pigs may be equally thwarted in light of nonvital benefits is even more contestable. We have not provided a conclusive answer to that question. However, with respect to the arguments of capacity-based dignity, one possible solution is to limit nonvital therapies to cellular-based xenotransplants, the cells of which can in principle be procured from fetuses during a specific developmental stage in which they are not yet able to experience suffering altogether.

11.1.2 Harm to persons

A trade-off of interests is much less appealing, however, when harm to other, non-beneficiary, *persons* is at stake. The risk that a xenograft carries an infectious agent that will be transmitted to others than the xenotransplant recipient cannot be excluded. The size and nature of that particular risk - whether it be a harmless influenza or a fatal pandemic, the range in between, or neither - and the probability that any of those scenarios will occur, are essentially uncertain and unquantifiable. At worse, xenotransplantation may affect the health and lives of the global population. That constitutes a severe intrusion on the 'harm principle', which generally leads us to conclude that duties not to injure others are more compelling than duties to prevent harm or to provide benefit. Harming others for the benefit of xenotransplant recipients thwarts their interests to be treated as autonomous agents and to receive an equitable distribution of benefits and burdens.

It is conceivable that a part of the population is willing to 'consent' to the potential harm involved in xenotransplantation. Those people may recognize that it is to everyone's advantage that progress in the treatment of diseases and in the prevention of mortality is pursued. They may also accept that they themselves may come to depend on replacement

technology in the future. Another part of the population, however, may not accept that risk. Indeed, it is reasonable to accept that this will foremost be the case for those who will not be able to share in the benefits. Particularly problematic in this respect is the population of the developing world that does not even have adequate access to the most basic health care and lacks the financial means and infrastructure to monitor and control possible zoonotic outbreaks.

Many regulatory bodies across the globe nonetheless do not wish to preclude the development of clinical studies. They respond to the public health threat by establishing various measures that would make the spread of a zoonosis highly improbable. As such, xenotransplantation research must proceed with proper national oversight, organized international cooperation and adherence to universally-accepted, high standards of oversight and surveillance. The surveillance is ultimately dependent on the screening of source animals and on long-term monitoring schemes of xenograft recipients (and to a lesser extent, of their contacts and the health care and nonhuman animal care workers involved). It is admirable that those measures have been addressed with such diligent concern by those who are themselves involved in the xenotransplantation research and industry. However, that approach in turn undermines the therapeutic intent of the clinical research. Moreover, it cannot warrant absolute protection of public health.

Current guidelines for clinical xenotransplantation require that prospective xenotransplant recipients consent to an ‘unknown risk’ of virus transfer as well as to constraints of their freedom in order to safeguard public health. We have indicated various reasons why that is problematic.

Xenotransplantation is still highly experimental and all forthcoming applications will be clinical *trials*. As with all experimental therapies, xenotransplantation trials will involve a certain burden of risk that challenges the therapeutic value of the procedure. The risks include potential physical harm directly related to the surgical procedure, adverse effects involving the physiological incompatibilities between the xenograft and the host and immunological rejection of the xenograft. Moreover, if tolerance induction is lacking, xenografts will only survive with increased immunosuppressive regimens. That may incur greater health burdens than the complications that commonly arise from immunosuppression following an allotransplantation. Other risks, such as the formation of tumours, are also conceivable. Xenotransplantation may evoke extra difficulties to adjust to the xenograft psychologically, which, we claimed, can further distort the quality of life

and may increase the chances that the medical recommendations will not be observed properly. Furthermore, all xenotherapies imply a risk of zoonosis. Those risks are less pronounced in the case of cellular xenotransplantation, but nonetheless not excludable.

Clinical trials must first and foremost be in accordance with ethical codes and rights regarding experimentation on humans. The general norm on clinical experimentation dictates that physicians should abstain from engaging in research projects involving human subjects, unless they are confident that the risks involved can be satisfactorily managed, or unless the risks are reasonable in relation to the potential therapeutic benefits. As noted in Chapter 4, there is uncertainty at what point the risks can be regarded as reasonable in order to proceed with clinical trials. Nonetheless, the risk of zoonosis renders the balance of expected therapeutic benefit over potential adverse effects on the subject's wellbeing increasingly implausible. It may be in the interest of a patient to engage in some form of risk-taking, particularly when the stakes of the trial are high (when it offers a potential to save his or her life). If the transplant provokes a life-threatening infection, however, the alleviation would be only temporary. Moreover, the safety requirements imposed on future xenotransplant recipients imply an additional burden on the therapeutic value of xenotrials. Requiring a xenograft recipient to consent to a long-term regime of extensive surveillance, before there is evidence of a health hazard, would involve a setback of significant psychological interests for the recipient - and conceivably, for the close contacts in his or her social environment as well. As evident from our discussion of the psychological effects of xenotransplantation, it will be important to minimize the recipients' awareness that they are 'not normal'. Being subjected to life-long monitoring will not be advantageous in that respect. Furthermore, the consent requirements involve infringements of an individual's rights to non-interference in personal affairs and private life, the protection of confidential information and the right to withdraw from an experiment at any time. It is important to note that those requirements will apply even if the xenograft is rejected and replaced by a human substitute⁵.

The Council of Europe has clearly stated that, in light of the public harm to be avoided, consent can justify the waiving of these rights⁶. Nonetheless, it is questionable whether the level of uncertainty inherent in xenotransplantation can be fully regardful of informed choice. Also, it has been proposed that the first trials should be reserved for patients with serious/life-threatening disorders, who have no alternative treatment options⁷. Such patients will be desperate and, hence, more vulnerable to what can be called "voluntary incompetence"⁸. It is also highly ambiguous whether we can expect recipients to limit

their *future* autonomy in the various ways that xenotransplantation involves. The argument can be made that it is part of one's duty as a patient to adhere to the recommendations. Indeed, contemporary medical and bioethics literature is increasingly attentive to the issue of patient responsibilities⁹. Nonetheless, it can be expected that consenting recipients will not be willing and/or able to bear that responsibility at a certain moment. We have referred to the high rates of non-compliance to health recommendations after an allotransplantation in that regard. Furthermore, for non-urgent xenotransplant interventions, individuals may come to regret their consent in the awareness of advances of alternative technologies that do not impose restrictions on their freedom¹⁰.

In order to protect public health, then, it will be necessary to *enforce* adherence to a person's prior consent against his or her later wishes. Even if it can be argued that such enforcement is ethical, legally effective means to ensure adherence prior to a demonstrable state of public health emergency have not been set in place. Infectious disease is the predominant concern of public health and forcible isolation of infected individuals goes back (at least) to cases of leprosy in the Middle Ages¹¹. However, enforcement of public health measures is dependent on evidence that the individual has in fact contracted an infectious disease and poses a public health hazard¹². Current public health law provisions cannot enforce long-term surveillance when the recipients are asymptomatic and the nature and communicability of possible pathogens is undetermined. It is also conceivable that transplant centres themselves will brush aside the stringent (and costly) surveillance, particularly in nations that do not have appropriate national oversight in place. There is currently an agreement that the results of trials that breach xenotransplantation guidelines should not be accepted for publication in high-ranked peer-reviewed journals. Apart from that, however, there is currently no international sanction for non-compliance to international xenotransplant guidelines, nor, for that matter, an authority to impose the sanction.

As a solution to those problems, we argue that, if there is to be any level of international cooperation on xenotransplantation regulation, it should foremost oversee that all trials await further evidence of non-infectiveness. That approach would compensate for the practical flaws and ethical problems related to post-transplant surveillance.

11.1.3 Out of harm's way?

As we saw in Chapter 8, the constraint against doing harm to others is not a moral absolute. It is rather a function of the size and nature of the danger that is exposed in order to bring about good results, and the probability that the harm will occur. In light of such an assessment, activities that involve risk of life - such as using public transport or even living organ donation - are permitted. In lack of sufficient descriptive components for a science-based risk assessment, however, the permissibility of the risk of xenogeneic infection depends on an individual and social normative basis. In comparing the analogies of the emergence of antibiotics and the development and study of recombinant DNA technology, we saw that the permissibility of health hazards posed by (bio)technologies is co-dependent on a) the perception that the potential benefits are both substantial and attainable, and b) the responsibility to take into account those aspects of risk that have a foreseeable effect. Studies suggest an overall, growing acceptance of xenotransplantation among the general public over the past decade^{13,14,15,16,17}. If we can thereby presume that the first condition can be fulfilled, it will still be of crucial importance to fulfil the remaining criterion. The underlying reason would seem to be that, in developing hazardous technologies, we are in the position to annul foreseeable adverse consequences in advance and thus have a particular moral responsibility to do so. Given that the lifelong monitoring requirement is a weak guarantee that the foreseeable risk of xenogeneic virus transfer will be excluded, it is essential that pre-clinical research further identifies and excludes the infection or recombination potential of detectable organisms from the source animals before proceeding with clinical trials. In this regard, there is enthusiasm about the progress that has been made - and can continue to be made - in identifying and defining the infectious potential of most known porcine pathogens. Breeding and immunocompromised cloning may also further reduce infectiveness¹⁸. Ongoing research in the use of semi-permeable membranes and genetic alterations provides a particularly optimistic prospect of precluding transmission for cell-based xenotransplant products.

Pre-clinical methods will not exclude the possibility that *undetectable* organisms will be transferred along with the xenograft. Nonetheless, *if* the risk of xenozyoonosis is reduced to a merely *theoretical* risk, it would be far from clear why that would require more stringent control measures than risks originating from 'natural' causes. Our approach reduces the main responsibility for risks to those investigators who develop the technology and to the damages they foresee in their studies¹⁹.

Pre-clinical research with animal models may, however, have its limits. Nonhuman primate models may not provide conclusive data on how humans will react to a xenograft and to potentially infectious agents. Ideally, we suggested, the foreseeable risks before trials involving human subjects would be addressed through experimentation on PVS bodies in case of willed body donation. It would be morally preferable to acquire proof of safety from experiments on a 'non-person human being' rather than on a living patient. Indeed, in light of our concept of capacity-dignity, that is even morally preferable to the ongoing use of primate models (we will discuss this further at the end of this chapter). If the prior person in a PVS had, when competent, consented to participate in such trials, using their bodies for clinical trials of xenotransplantation is no more controversial than the range of uses to which we currently put cadavers in research and in the training of surgeons. For lack of such a scenario, and if the potential infectiveness of even detectable agents cannot be *entirely* precluded by existent pre-clinical methods, it will be essential that the pre-clinical investigations are as extensive as possible. Triller and Bobinski indicate a difficulty in such reasoning. A focus on foreseeable aspects of the xenozyoonosis risk could limit the initiative to study all possible adverse side effects on public health²⁰. In light of this concern, stringent oversight at that level of research will undoubtedly remain necessary.

It should be clear that by focussing on *detectable* infectiveness, the interests of the prospective patients can be better met. Some level of physical risks is by definition part of a xenotransplantation experiment. Indeed, trials will be the ultimate step in fully ascertaining the potential risks of xenotransplantations. Nonetheless restricting (or, ideally, excluding) the possibility that known viruses will unleash an infection in the recipient is an important aspect of enhancing the therapeutic value of the trial. Furthermore, that approach should ease the requirements of long-term and intensive monitoring. It will remain important that the xenotransplantation patient is informed of the theoretical risk of xenozyoonosis. It will also be beneficial for both the recipient and the public at large that some samples are taken prior to and directly after the xenotransplantation and that public health authorities are notified as soon as possible in case adverse events occur. Furthermore, some lifestyle restrictions are unavoidable. In particular, it would be unadvisable to let a xenograft recipient donate blood, tissues or organs. Nonetheless, the need to enforce long-term surveillance will not be that essential. In our view, easing the surveillance requirements will facilitate acceptability of using xenotransplantation for children, who are generally not regarded as acceptable recipients during initial trials.

We also argued that, if the risk of xenozoonosis were reduced to a merely theoretical threat, that would provide a proper basis for addressing global health injustice. The problem of global health injustice is not unique to xenotransplantation but increasingly merits consideration. The growing gap in health care outcome, on a global scale, is “the unmentioned elephant in the room of medical ethics”²¹. Martine Rothblatt has provided the most ambitious and well-considered approach to counterbalance the inequitable distribution of burdens and benefits related to xenotransplantation. In ‘Your Life or Mine’, she argues for the necessity of a *global buy-in* of the developing world²². In order to protect all nations universally against a potential xenozoonotic outbreak, randomized blood sampling should be conducted in those parts of the developing world that lack resources to perform effective xenozoonosis surveillance. In exchange, those nations must be offered basic health care support. In addition, they should be given partial access to xenotransplants. The way to implement such a ‘geo-ethical approach’, according to Rothblatt, is by creating a mandatory global oversight, regulation and follow-up organization, which she calls ‘GEOX’ (Global Enforcement Organization for Xenotransplantation), the activities of which could be financed by taxes on the pharmaceutical companies per xenograft sold.

The need to augment global access to transplant activities is incontestable. In many developing countries, transplantation is the only type of renal replacement therapy available²³, while the transplant rate is less than 10 per million population (in contrast to 45 to 59 pmp in the developed world)²⁴. That figure covers only 2 per cent of the estimated need²⁵. Whether the permissibility of xenotransplantation is also dependent on global access to basic forms of health care, however, is less compelling. In particular, it is unclear to what extent GEOX could contribute to ‘basic health care’. According to the 1978 Declaration of Alma-Ata, for instance, basic health care treatment would include promoting appropriate nutrition, access to clean water and essential medicines, maternal and child health care, appropriate treatment of common diseases and injuries, control of communicable and endemic diseases, and access to basic sanitation²⁶. Rothblatt’s aim must be modest if the expenditure of \$13 per capita in low-income developing countries, the amount she estimates to be generated by GEOX taxes²⁷, is to suffice.

Xenotransplantation is not the unique stepping stone for the weighty responsibility of addressing the needs of the least well-off on a global scale. Indeed, in light of the greatest disparities of global health care, there is more reason to set up a Global Enforcement Organization for Pandemics (GEOP) rather than a Global Enforcement Organization for

Xenotransplantation. Infectious diseases constitute the greatest cause of mortality in the developing world (see chart in Chapter 1) and continually emerge, in ever new forms, as global public health threats. The theoretical risk of zoonosis serves as a reminder of the urgency to deal with the persistent manifestation of existing and emerging zoonoses, regardless of their cause. It is interesting to note in this respect that, in July 2004, President G. W. Bush signed into law 'Project BioShield'. That project allocates \$5.6 billion over 10 years to disease surveillance and research and development of vaccines and drugs for smallpox, anthrax, botulinum toxin, Ebola virus, plague and other pathogens and infections²⁸. Although that budget is primarily intended for biodefence, it is indicative of an increased sensitivity to the threat of new and re-emerging infections. The enormous investment in the protection of the US public health, however, contrasts sharply with the lack of resources of the WHO²⁹, which has the expertise to respond rapidly to an infectious outbreak on a large scale (as evident from their response to the emergence of SARS and Influenza A/(H5N1)).

11.2 Discussion

Our account of how to balance the unique risks and harm involved in xenotransplantation is not uncontested. Both direct criticism on our writings and indirect objections found in the literature (and thus far not dealt with) appear to challenge three pillars of our argumentation:

- (1) that it would be wrong to allow patients to consent to trials at the current stage of development and under the current regulations;
- (2) that the use of PVS bodies is an ethical solution for the possible difficulties in acquiring more proof of safety;
- and most fundamentally:
- (3) that *if* xenotransplantation proves to be successful, the overall benefits of this procedure will be immense.

In the following, we will address the objections to those most fundamental presumptions and attempt to provide additional support for our approach.

11.2.1 Xenotransplant trials: a guinea pig race?

Our analysis of the permissibility of potentially harming patients and public health implicates the need to hold off clinical trials until more is known about the associated infectious disease risk and until the foreseeable aspects of that risk can be excluded as much as possible. However, in light of the potential benefits of various applications, it may be argued that xenotransplantation trials must be conducted as soon as possible.

Solid organ xenotransplant trials

This is the approach Neil Levy has taken in criticizing our proposal to test solid organ xenotransplantation on consenting PVS bodies rather than on living subjects. The appendices to this dissertation include both his commentary and critiques by three other authors. Those three other critiques will be discussed in the next section of this discussion.

According to Levy, patients currently facing death would gladly accept the risks and harms in exchange for a chance to lengthen their lives, however stripped of fundamental rights³⁰. If a xenotransplant is their only chance at avoiding death, so he argues, patients have the right to choose that option at the cost of some or even all of their rights. He indicates the paradoxical consequences if our proposal were implemented:

A patient suffering from a terminal illness might volunteer to participate in potentially life-saving xenotransplantation clinical trials. The scientists conducting these trials would be forced to respond: “we cannot use you now; make a living will and perhaps we shall consider you once you die”. The patient is assured that her rights will be respected, but this seems to me small comfort.³¹

We share Levy’s concern for the desperate situation of the many patients who are currently staring death in the face in lack of an organ transplant. We can also accept that extreme cases may require extreme measures. Moreover, there is little ground for objecting to the claim that a person may waive his or her rights if he or she is fully aware of the resulting consequences. A strong defence of personal sovereignty, which will grant autonomous beings the right to act in such a way that is of harm to them - even when the decisions imply an alienation rather than fulfilment of autonomy - has been embraced by other authors in this respect as well. Hughes, for instance, argues that the patient’s autonomous choice with regard to xenotransplant treatment ought to be respected, if that choice affects his or her own interests only³².

We discussed the difficulties of enforcing the long-term implications of consent above. Moreover, post-xenotransplantation surveillance does not only affect the interests of the willing patient, but also of the people closest to him or her. Close contacts will also be monitored and the recipient and his or her partner may be advised to use barrier contraception and to refrain from pregnancy. Still, we can grant that the recipient's spouse and family will accept the safety requirements in exchange of an opportunity to save their beloved one. Notwithstanding that, more arguments are required in order to defend the scenario Neil Levy suggests. For one, his aim to benefit the patients is one of groundless optimism. Two, by accepting hasty applications on desperate patients, it will prove extremely difficult to avoid a problematic turn away from ethical considerations meant to safeguard patients involved in clinical trials.

The experiments we suggested in our original article were of a nontherapeutic nature, for want of results that demonstrate whether solid organ xenotransplantation will be sufficiently safe for trials with patients. In light of the limited survival periods of pre-clinical animal models reported to date, there is insufficient reason to assume that the procedure can support human life. The suggestion to take the plunge towards xenotransplanting solid organs in patients - without indications that we have arrived at the stage in which we can expect the patients to benefit - conflicts with the requirement that clinical research must establish, either from pre-clinical or prior clinical research, that the expected benefits outweigh the risks of the procedure³³.

Without a risk/benefit balance, Levy's suggestion implies that, at whichever research stage, the slightest chance that patients with no alternative could benefit, is deserving of a trial run. That leaves the door open to various situations in which people beyond hope volunteer for unwarranted and questionable 'therapies'. Not only is it not always clear cut that certain patients have no alternative, it is also highly questionable whether their 'informed consent' is a sufficient condition. Problematic research in the past has indicated that desperate people will consent to almost anything. In such a way, patients are made vulnerable to experiments with purposes other than purely medical-scientific ones. Levy's criticism appears to imply that reluctance to conduct experiments on terminal patients at a premature stage is what ultimately causes their death. It would be wrong to suggest such a direct connection. There is indeed a real chance that patients die while in effect they could have been helped by hasty trials, but that is the price we pay to protect the patient population at large against malpractice and irresponsible research. Also, as emphasized by

the International Xenotransplantation Association Ethics Committee, if the first trial recipients of solid organ xenotransplantation attain substantial longevity and quality of life, that will enhance public acceptance of the field³⁴.

Ex vivo and cell-based xenotransplant trials

In contrast to solid organ xenotransplantation, there is more optimism regarding the efficacy of extracorporeal liver support and cellular xenotransplantations, which have provided the most recent clinical applications. Enthusiasm regarding those procedures has also raised the argument that, by further withholding clinical trials, patients are denied urgently needed life-prolonging or quality of life enhancing options³⁵.

However, it is agreed that, given the current level of risk, xenotransplantation should not be conducted if other procedures of comparable effectiveness are available for the patient³⁶. While past experiments with extracorporeal pig liver perfusion and bioartificial liver devices have successfully bridged patients to transplantation, we noted in Chapter 4 that there are no convincing data on the clinical efficacy of those approaches or their advantage over conventional intensive care therapies.

Similarly, in 2001, Diacrin/Genzyme (a joint venture for the development of cellular therapies for Parkinson's and Huntington's diseases) announced that the results of a phase 2 trial involving neural xenotransplantation showed no difference in outcome between the ten patients treated and the control group³⁷. By contrast, recent trials involving pancreatic islet xenotransplants do indicate promising results in terms of a decrease in the recipients' exogenous insulin requirement. It is those trials that the above quoted defenders of urgent trials are primarily alluding to. Nonetheless, here too, there are various reasons why the eagerness to proceed with such trials may be ill-considered.

For one, the procedures and results of such trials are very controversial. Rood and Cooper³⁸ have reviewed the four most recent reports on clinical trials involving porcine islet xenotransplants^{39,40,41,42}. They were not performed in accordance with some of the principles set out by the International Xenotransplantation Association Ethics Committee. The islets were not always procured from specified pathogen-free pig herds and there were not enough indications of appropriate oversight of post-transplant infectious organisms. Furthermore, no pre-clinical data from nonhuman primate models were reported. While experiments on nonhuman primates cannot provide conclusive indications of how humans

will react to a xenograft, positive results of such pre-clinical models would nonetheless have given some support of the trials' reported outcomes. Without such results, Rood and Cooper note, the decrease in patients' insulin requirements could just as well have been obtained from the improved medical follow-up of their condition.

Second, it is questionable whether the potential recipients themselves will, at this stage, advocate access to islet xenotransplantation trials. In 2005, Deschamps *et al.* published the results of a survey that aimed to assess the willingness of 214 Type 1 diabetic respondents to receive pig islet xenografts⁴³. It was found that reluctance towards the use of xenotransplantation as a therapeutic option grew as the respondents became better informed of the risks associated with the treatment. While 52 per cent of the patients were willing to receive pig islet xenografts at the onset of the questionnaire, 70.5 per cent of the respondents ultimately opted out in response to the final question. Deemed most worrisome were "the risk of disease transmission" and "risks not yet identified". We were surprised to learn about that notable refusal rate. It conflicts with some prior assumptions we made with regard to public perceptions of xenotransplantation. The desire for applications of animal graft transplants is conceivably (and also demonstrably, as pointed out by the authors themselves) largest among those people most likely to benefit from such a treatment. And while most people, if given the choice, would currently opt for an allograft rather than a xenograft, we found it reasonable to assume that acceptance of cellular xenografts would be relatively high in comparison with vascularized organ xenografts⁴⁴. Especially astonishing is that the results of Deschamps *et al.* contrast with the largely permissive attitude towards the use of pig islet-cells for Type 1 diabetes (82.1 per cent) found among different population groups (n = 942) in the Dutch-speaking part of Belgium⁴⁵. The results also contrast with a previous comparative survey conducted by Deschamps and published in 2000⁴⁶. In this study, more than half of the 697 adult representatives of the French general population and 64 per cent of the 377 adult Type 1 diabetic respondents were favourable to receiving a xenograft. As to why the more recent survey reveals such a considerable disinclination, Deschamps *et al.* stress the role of full disclosure of the risks involved. Naturally, it would be difficult to determine that only in the recent survey respondents were sufficiently informed so as to be able to fully grasp the potential dangers involved with xenotransplantation. Nevertheless, the negative effect of knowledge about and the positive effect of ignorance of the risks on the acceptance of xenotransplantation have been observed elsewhere^{47,48,49}. Indeed, the largely permissive attitude of the respondents in the Belgian study could be partly ascribed to their being only briefly informed of the risks. Furthermore, while we do not rule out that numerous

surveys have included sufficient information on the risk of transmitting zoonosis, the recent Deschamps *et al.* survey explicitly cited risks relating to immune rejection, uncertain efficacy and of infections and cancers, amongst other “unknown risks”. Understandably, people are not willing to solve a problem via measures that potentially create an even greater problem. The benefit they most desire is the discontinuation of insulin injections. For 73.5 per cent of the respondents, that was the principal reason to opt for xenotransplantation, before limitation of complications (52.5 per cent) and increase in life expectancy (44 per cent). While their condition can be controlled by treatments already available, they would prefer an alternative treatment that would relieve them of the ceaseless and unpleasant need to maintain target blood glucose levels. That benefit does not compensate for the potential risk of immunosuppression-related infections or cancers (which only 6.7 per cent of the respondents were willing to accept). Patients with Parkinson’s disease, for whom such relatively successful alternative treatments are currently lacking, do have a more permissive attitude towards xenotransplantation, despite their being informed of the potential virus risk⁵⁰.

Third, it is not at all clear whether the recipients of the recent islet xenograft trials mentioned above consented to the procedure fully aware of the risks. Valdés-González *et al.* have been criticized for their particular choice of recipients⁵¹. The published report notes that the recipients were twelve adolescents, whose mean age was 14.7 years (range 11-17)⁵². Particularly the younger children may be incompetent to fully acknowledge the magnitude of the risk involved. (Furthermore, according to verbal reports, the recipients were street children, which would imply that they were desperate to be helped.) The report gives no indications of the level of information the recipients received prior to the transplantations. We were not granted leave to inspect the consent forms and thus cannot confirm these worries, but there is sufficient ground for suspicion.

In short, we feel that postponing clinical trials until more pre-clinical data are acquired, is justified.

11.2.2 The use of non-persons as experimental models: a body at will

Whether or not research on bodies in a permanent vegetative state is an acceptable model for acquiring ‘pre-clinical’ data, however, is a different subject of criticism. Steven Curry, Heather Draper and Janna Thompson and Robert Sparrow have expressed three crucial

objections in this regard^{53,54,55,56}. A first objection from the authors is that the permanent vegetative state either cannot or should not be regarded as death. Second, the argument is held that prior consent to willed body donation in case of a PVS is less deserving of respect than the wishes of surviving relatives. A third objection is that we are inconsistent to require prior consent for such a donation altogether, because our motivation is utilitarian and focused on the interests of the greater good only.

The status of a PVS ‘patient’

As for the first objection, we are said to believe that “PVS patients are in fact dead”⁵⁷. Some of the commentators hold this claim to be factually untrue, leading them to argue that we are dealing with living patients, “albeit with a very poor quality of life”⁵⁸. Alternatively, it is said that this claim is logically inconsistent with the way in which we leave room for subjective judgement⁵⁹.

In response to whether “PVS patients are in fact dead”, we want to give the following remarks. Speaking of a ‘patient’ in a permanent vegetative state (let alone, of a ‘person’ in a permanent vegetative state), is a contradiction in terms and impedes the discussion. We argued that the word ‘patient’ is inappropriate in relation to the condition, because it generally refers to a living *person*, whereas the bodies we conceive of are permanently devoid of all forms of personhood, even of the minimum requirement for the capacity for personhood, while the body is still *biologically active*. Given that the *person* no longer exists, it makes sense only to speak of - indeed, living - *bodies* in a permanent vegetative state.

That the person is dead while the body remains alive is the *sine qua non* of our proposal. It is neither a matter of opinion nor a matter of ethics. That a *demonstrably irreversible* vegetative state implies that the person has died leaving behind a living human body is a matter of *fact* which is in keeping with the specialization of the brain (see, for instance, cerebral cortex versus brain stem function).

The fact that a person in a demonstrable and irreversible permanent vegetative state is dead, then, explains why we cannot accept the alternative justifications of PVS experimentation that have been suggested by Steven Curry and Heather Draper. According to Curry, provided that prior informed consent was sought, ‘living PVS patients’ may be enrolled in xenotransplantation experiments - just as healthy subjects may enrol for Phase

I and II drug trials - because they are ‘in exactly the right kinds of ways’ not like other patients:

It just so happens that PVS *patients* do not have any of the interests listed by the authors. *Persons* who are in a PVS will never wake up, they feel no pain or discomfort, and have no continuing interest in their *own* survival. Even if one thinks that PVS *patients* have a right to life (on even the most contentious meaning of this term), these *patients* must also have a *right* to *risk* that life for the common good.⁶⁰ [our italics]

Similarly, Draper argues that if an individual in a PVS wishes to participate in xenotransplantation research, this is a matter of “life-style choices”, a matter for him or her alone⁶¹. The authors believe that that move bypasses the need to agree on whether or not they are dead while maintaining the motivation to use bodies in a PVS.

In effect, however, these claims miss the point and do not provide a more solid justification of our proposal. Persons, when in a permanent vegetative state, cannot decide to risk their lives for the common good, for there no longer is a person that can consider taking a risk. They can only decide in advance (t1) - and to a certain extent - the fate of their body once they, as a person, cease to exist (t2).

We can distinguish various prior decisions of the fate of one’s body at t2. These include both decisions to keep the body alive or to let it die. In the latter case, the body becomes a cadaver and prior wishes concerning the retention of a corpse become applicable. In the case in which the body is to be kept alive, one can choose to either have it left untouched, or - the option that we open up - to donate it for research purposes. The question that remains, then, is whether such fate is acceptable for a living body.

The response to that question depends on the value that can be attributed to a living, yet person-void, body. In other words, is the death of the person essentially sufficient to allow that the body is treated as a corpse? It is with regard to that question only that we leave room for subjective judgement. That is because it relates to the *definitional* or *conceptual* level of the concept of death. As stated above, the question whether or not a person is dead, is a matter of fact. That particular question relates to the criteriological and medical diagnostic levels of the concept of death, which are essentially a matter of natural sciences⁶². The definitional level, by contrast, is subject to philosophical and theological beliefs. That explains why people may hold different understandings of what it *means* for a human being to be dead.

That there can be very different understandings among people of how to define death does not mean that there are no limits to which concepts of death can be implemented. If that were the case, we would indeed need to accept an endless possibility of alternative definitions of death, as one commentator points out⁶³. Nonetheless, we do feel that it is reasonable to claim that the death of the person is a sufficient condition of what it means to be dead. The reason for that lies in the common ground with the current concept of brain death. It is the irreversible loss of consciousness and thus of any capacity for personhood rather than loss of brain stem functioning that lies at the basis of accepting whole brain death, which was prior to involvement of the interests of the transplant field characterized by ‘le coma dépassé’. Death of the person is the necessary condition of having certain wishes with regard to treatment of the body met, and that is by definition the case for both whole brain death and cortical brain death.

Conflicting interests between the dead and the living

Janna Thompson, in stating her reluctance to treat PVS bodies as dead, contests that conceptual consistency. According to her, treating PVS bodies in the manner we suggest would cause the public to reach the ‘breaking point’ given the current tensions between social and medical perceptions of death⁶⁴. It is unclear how Thompson can know this to be so, for she gives no indications to support her claim. The general and important point that she makes, however, is that use of PVS bodies for research purposes would cause great discomfort and inconvenience for the surviving relatives, an issue we also raised, and the significance of which we do not mean to undervalue. Nevertheless, the idea that this inconvenience and distress should overrule the prior consent concerning the body in a PVS, raises the question as to what the value of personal autonomy and informed consent of a person at t1 is and to what degree it must be respected at t2.

Thompson is outspoken in defence of the idea that ‘the wishes of the deceased’ are less deserving of respect than the wishes of surviving relatives and may thus be discarded⁶⁵. Most of the other authors would seem to agree with that view. It is however confusing to speak of the ‘wishes of the dead/deceased’ (or, alternatively, of the ‘right of the living dead’) and to use that claim as the starting point for morally weighing the significance of those wishes. The dead have no wishes to be (dis)respected. Rather, what is at stake is the right of the *living* to decide in advance when and how to be treated as dead and the question of whether that prior decision should be respected after the person has died.

The default position, that testamentary wishes should be respected to a certain degree, is generally limited only in those cases in which honouring these prior wishes would disrupt other values or judicial requirements without a counterbalance. For instance, a desire to display one's decomposing cadaver in a public area as an artistic statement would disrupt the tradition-bound value of properly putting a body to rest, and is not counterbalanced by the satisfaction that would result from this exposure. That does not mean, however, that there are no circumstances under which one's cadaver can be publicly exposed; on the contrary, there can be very good reasons to do so. In the 'body farm' (officially known as the University of Tennessee Forensic Anthropology Facility), bodies lay to rest in the open as a source of information for the science of decomposition⁶⁶. The results of that research allow a more accurate understanding of the process of decomposition and thus a more precise determination of the time of death, which is crucial to crime-solving.

While our suggestion may disrupt the value of properly putting a body to rest, there is also a weighty counterbalance. The use of a body in a PVS would serve a great societal purpose, comparable to the purpose that impelled the shift in policy to the whole brain death standard (making organs more available for transplantation). This is not an outrageous thing to wish. The family will know exactly where the body is located and what will take place. If the desire to offer one's living body to science in the event of a permanent vegetative state is discussed with family members in advance, the surviving relatives need not necessarily be distressed. In fact, the relatives may even be consoled by the body donation of the deceased person, in that it gives some meaning to the death and that the donor will be remembered for his or her nobility and altruism. Moreover, Thompson's concern that the bodies cannot be put to rest in an appropriate manner should be equally of concern with regard to current postmortem body donation, for which a body may be kept for up to three years.

Prior consent and the greater good

Robert Sparrow raises a third objection to our suggestion. He questions the role we attribute to prior consent in light of our motivation to promote a public benefit. He claims that we cannot but conclude that the prior consent is outweighed by the sum of benefits the research on their bodies would produce for the general public (and the patient population, more specifically). In light of these greater benefits, Sparrow argues, our arguments should not rely so heavily on explicit consent. They should rather endorse

presumed consent or even a full discarding of the moral significance of consent. Within a consequentialist perspective, it should be irrelevant whether or not the research is conducted in accordance with the prior wishes, so he argues.

It is, however, not true that a utilitarian motivation must support the implications that Sparrow lists. For one, the radical utilitarianism that Sparrow conceives of would not, in a utilitarian calculation, bring about the best consequences. In analogy with a popular thought experiment, in which an angry mob is desperate to find and punish the unrecognized offender of a severe crime, sympathisers of consequentialist motivations do not necessarily have to accept that a sheriff *must* turn over an innocent man in order to avoid a public riot. One can still choose not to turn the man over because of a realistic anticipation that it would not bring about the best consequences (consider, e.g., the riot that would arise when the mob finds out that justice has not been served). Similarly, the distress that would arise from disregarding the wishes of a prior person would not be a better alternative than limiting experimentations to bodies that have been donated in consent. Moreover, it is wrong to presume that there can be no principle-based restrictions on utilitarian calculations. If our argumentation lacked any principle-based approach, we would not have arrived at the proposal to begin with, for we would not be looking for ways to avoid the ethical problems that arise in using patients as research subjects. We stand by the principle of personal autonomy and do not agree that it can in this case be thwarted by public benefit. We can defend presumed consent if it is in accordance with respect to personal autonomy, in other words, if the public does in fact largely consent and know that the consent is being presumed in absence of an explicit objection. That is certainly not the case at this stage of our suggestion. Defence of carrying out the research without or against the willingness of the prior person is out of the question.

11.2.3 The ‘greater good’: critical notes

Our argument to use PVS bodies as research models is not driven by an *ultra*-utilitarian argumentation. It is nonetheless illustrative of the fact that we have gone to great lengths to find acceptable conditions under which xenotransplantation may proceed, rather than to preclude its development altogether. Our arguments have been driven by the anticipation that, if xenotransplantation will one day be successful, the overall benefits of this procedure will be immense. Most importantly, an unlimited supply of transplantable

grafts could, in principle, annul the current difficulties of ensuring equitable access to life-saving and/or quality of life enhancing transplant activities.

However, various arguments have arisen in the literature, which appear to undermine the appeal of producing an unlimited supply of xenografts in terms of that benefit. The concern exists that xenotransplantation will close the gap in the 'duty of equity' only to open another. Two scenario's can be distinguished in this regard:

on the micro-level, it is possible that, under certain circumstances, solid organ xenotransplantation will not enhance equitable access to transplant activities;

on the macro-level, it is questionable whether focus on augmenting the transplant rate through xenotransplantation is a justifiable expenditure of health care resources, with regard to other health care options.

We will not address those concerns in depth, as we lack sufficient data to fully investigate the possible organisational and financial implications of a procedure that has not yet been established. Nonetheless, it is worthwhile to mention those considerations, because they indicate the specific conditions under which the benefits of xenotransplantation will truly be substantial.

11.2.3.1 Barriers to equity on the micro-level

A particular problem arises with the possibility that xenotransplantation will turn out to be no more than a temporary solution for patients with end-stage organ disease: a bridge to transplant. That is the primary utility of *ex vivo* perfusion techniques. The *in vivo* implantation of solid xenogeneic organs may also prove to be of limited duration, at least during the initial trial phases, if specific immunological rejection and physiological incompatibilities cannot be sufficiently overcome in advance. If xenotransplantation were merely to develop as a bridge to transplant, that would imply that the waiting lists for a human organ would not decrease, rather on the contrary. Patients would become eligible for a human organ transplant, whereas without the temporary xenograft, they might not have survived.

The same effect is expected for the use of totally implantable artificial hearts, at least in the early phases of routine clinical use. The Rathenau Institute has designed a quantitative simulation model to assess the effect of artificial heart transplantations on the waiting

list⁶⁷. The simulation model shows that, by introducing artificial hearts, the number of people on the waiting list decreases and waiting time is reduced. Nevertheless, it also shows that, temporarily, more people on the waiting lists will die if artificial hearts provide only a short-term solution than would be the case if the normal donor heart programme continued. That scenario results from the expectation that recipients of an artificial heart will, at some point, develop an acute need for an allotransplant. Given the urgency of the transplantation, those patients will be given priority on the waiting list, thereby directly lengthening others' time on the waiting list and indirectly affecting their mortality. Mortality will continue to increase unless the performance of the artificial heart almost equals that of a human heart. With a few exceptions (e.g. short-term liver perfusion may allow the liver to fully recover), it is reasonable to expect a similar increase in mortality when using xenotransplantation as a bridge to allotransplantation.

It is also possible that xeno-organs will be of suboptimal quality in comparison with allografts. In that case, too, the problem of just allocation is not solved, as there will be competition for the best organs⁶⁸. Xenotransplantation could thereby induce the same problems that occur in the allocation of marginal donor grafts. Alternatively, it is possible that quality will vary among the supply of xenogeneic organs and that access to the best quality xenografts will be inequitable. In that respect, it is important to note that xenografts will be purchasable health care 'products', the price of which will reflect the expenditures for research and development and for the patented techniques to produce genetically modified source animals in particular. The purchase will also cover the costs of ensuring that the pig herd is free of infectious disease, including requirements that relate to housing, breeding, feeding, medicating, testing and carcass disposal. Sanders Chae has suggested that the prices of xenoproducts could - within reasonable standards - vary according to differences in quality⁶⁹. The best quality xenografts could be charged the sharpest prices; suboptimal grafts could be made available at lower prices. If access to health care operates on the material principle of ability to pay, only the rich will be able to afford the best treatment options.

The fact that xenografts will be purchasable products also raises the concern that this will diminish the general motivation to donate one's organs altruistically. Although still highly controversial, we have given various arguments as to why lack of altruism does not necessarily diminish the moral significance of strategies that help to augment the transplant rate (see Chapters 2 and 3). In any case, concern over the fate of altruism should apply just as much to the emergence of other forms of graft-engineering.

Nonetheless, if large-scale use of purchasable transplant products were to decrease the rate of human organ donation, this could be highly problematic in light of the fact that xenotransplantation will not eliminate the need for human grafts altogether⁷⁰. Human organ donation will remain a necessary alternative in initial phases, but also in the long term, for patients who may never come to accept an animal-derived replacement graft or (with regard to the concern mentioned above) who cannot afford one. While we cannot predict the future impact of xenotransplantation on the public's willingness to donate, a direct (albeit perhaps minimal) adverse effect on the human donor potential will inevitably result from the vital requirement that xenotransplant product recipients and their intimate contacts (defined as those with whom the recipient risks exchanges of bodily fluids) do not donate any body parts for use in humans⁷¹.

Those concerns do not undermine the appeal for the use of xenotransplantation to save lives that would otherwise go lost. They rather indicate several conditions xenotransplantation must meet if it is to solve current problems of access to transplantation procedures. On the whole, it can be expected that problems of fair access to transplants can be avoided if the rescue through a xenotransplantation does not in itself entail subsequent rescue through an allotransplantation; if human graft donation remains encouraged; and if xenotransplantation does not introduce additional or inequitable financial restraints on transplant procedures. Whether or not the latter criterion can be fulfilled is for a great deal dependent on whether xenotransplantation will be made available by public health care resources and/or private insurance. It is at this macro-level of decision-making that the prospect of clinical xenotransplantation threatens yet another 'duty of equity'. The introduction of an unlimited supply of transplantable xenografts will imply an overall high rise of health care expenses. In relying on public or insurance funds, this will raise health care costs for all, ultimately raising the question whether xenotransplantation should have priority over other health care options.

11.2.3.2 Barriers to equity on the macro-level

Xenotransplantation: economic aspects

Clinical xenotransplantation will by definition result in a high rise of health care expenditures given the very intention to enable treatment of virtually all patients who require - or could benefit from - a transplant. Organ allotransplantation is one of the most expensive medical procedures available today. In the US, annually, an average of \$33,000

is spent on billed charges per organ recipient⁷². With inadequate graft supply, the transplantation rate is nonetheless a *de facto* rationed procedure, claiming not more than half a per cent of the total national health care expenditure⁷³. If all those in need of a transplant were to receive an allo- or xenotransplant, however, annual expenditures would rise from a conservative \$2.9 billion to \$20.3 billion, according to The Institutes of Medicine⁷⁴. That is likely to be an underestimate, given the possibility that xenotransplantation will entail a higher rate of *re*-transplantation, even when its utility transgresses the phase of providing a bridge to transplant. As the lifespan of a pig is 10 to 20 years, the survival of porcine organs may be much shorter than that of human organs. It is also conceivable that chronic rejection of xenografts will develop earlier than is the case for allografts. Furthermore, as mentioned above, xenografts may require increased immunosuppression even for such shorter xenograft survival. In light of the known effects of immunosuppression following an allotransplantation (see Chapter 1), it is conceivable that that will have adverse effects on the functioning of other organs. Also, the Institute of Medicine's estimate does not include the cost of cellular transplants and presupposes that the price per xenotransplant will be tantamount to that of an equivalent allotransplant.

Costs related to transplantation appear at three levels⁷⁵. During a first, pre-transplant phase, there are charges involving registration on the waiting list and evaluation and monitoring of the prospective recipients' health status. During the transplant phase, costs relate to graft procurement, surgery, hospitalization and hospital staff fees. The post-transplant phase induces varying costs of immunosuppressive therapy, follow-up and medical care of complication episodes. While it is difficult to estimate the expenses for xenotransplantation without the technology completed, it is reasonable to expect that it will increase the financial burdens at each of the above-mentioned levels.

The greatest savings xenotransplantation will offer concern the costs currently related to the pre-transplant phase. Successful xenotransplantation will avoid care during the currently long wait for a transplant, including pre-transplant life support and expensive ICU facilities. Indeed, it has been assessed that waiting list expenses constitute one of the major costs associated with kidney transplantation⁷⁶. Nonetheless, another cost factor is the screening of graft safety prior to surgery. Twenty percent of the costs of *human* kidney acquisition are related to pre-transplant laboratory costs⁷⁷. It has been estimated that testing each human donor for Human Immunodeficiency Virus (HIV), Hepatitis B (HBV) and Hepatitis C (HCV) currently costs approximately \$150⁷⁸. The rate of positive screening tests is 0.093 per cent for HIV, 0.299 per cent for HBV and 1.091 per cent for HCV. The total

cost of eliminating one potentially infectious donor is estimated to be \$4 million for HIV, \$2.6 million for HBV and \$2.3 million for HCV. If infectiveness cannot be completely precluded in the source animals, the screening of xenografts will be much more elaborate. Xenotransplantation will also require the drawing up of patient registries and the installation of blood and tissue archives. The costs of establishing a registry to archive samples from source animals and xenograft recipients are assessed at \$250,000 to \$300,000 a year⁷⁹. The archive itself would cost approximately \$1 million a year.

Pre-transplant savings will also be undercut by the higher costs of graft acquisition. As mentioned above, in contrast to human donated grafts, xenoproductions will have their price. It is currently uncertain what that amount will be (although critics estimate that the costs of pig organs may be as high as \$100,000⁸⁰). It is conceivable that the price of a xenograft will partly be dependent on the efficient use of the cells, tissues and organs from the source animals. Cellular xenotransplants are likely to be less expensive, particularly if a distinction is made between the species and the developmental stage of the source animals from which the cells are procured. Wright *et al* have presented a conservative measurement of the relative costs for xenogeneic islet transplantation from either transgenic tilapia or adult porcine donors⁸¹. The authors suggest that, on a per clinical transplant basis, the use of adult pigs as sources of islets would be at least hundredfold more expensive than transgenic tilapia islet production. For the use of adult pigs, costs of islet isolation per encapsulated islet xenotransplantation will exceed \$60,000 - expenses relating to the housing requirements not included. For tilapia fish, those costs are estimated at \$640. The authors did not compare the costs for islet retrieval from adult and neonatal/foetal pigs, but the latter (which we also prefer for ethical reasons) is also likely to be less costly.

The follow-up of xenograft recipients will also be more expensive than current post-transplant measures. In addition to the maintenance of patient registries and archives, infectious disease experts and staff will need to be hired to apply the long-term infection control measures. The expenditure on immunosuppression may also be higher, if xenotransplantation requires exclusively produced and patented drug regimens. There are also unpredictable costs associated with infectious disease outbreaks (note in this regard that the French government disbursed \$2.2 billion to compensate victims of AIDS-contaminated blood transfusions administered between 1980 and 1985⁸²).

Is xenotransplantation a health care delivery priority?

In Chapter 2, we noted that, for those who grant a positive right to transplantation medicine, its purpose must not be rationed for health care savings. Nonetheless, a ‘positive right’ to health care is a very problematic notion⁸³. Aside of the invalidity of the theoretical notions on which the concept is founded, it is highly impracticable to grant an individual a right to a particular health care product. Since the 1990s, there has been a dramatic and universal increase in economic pressure on health care systems. The crisis has been felt most clearly in the US, which witnessed an increase in gross domestic product expenditure on health care by 10.8 per cent between 1960 and 2004⁸⁴. By 2005, the country spent almost 15 per cent of its GDP on health care⁸⁵. All nations of the European Union, too, have been subject to an increase in health care expenditure over the past decades. Currently, the EU-15 spend 8.6 per cent of their GDP on health care (the average figure for the new member states is 5.8 per cent)⁸⁶. For every health care system, the primary factor associated with growing expenditures, aside of the longer life expectancy in aging populations, is the increased development and usage of medical technological innovations. More and more money is allocated to medicine because there are more and more biomedical breakthroughs. Governments, however efficiently they may manage their health care system, cannot accommodate every individual’s right to health. In particular, they cannot ensure, on an *a priori* basis, access to the benefits of all emerging technologies. Efforts to cover expenses for emerging technologies drive up health care costs for all. The increasing supply of medical therapies has also resulted in an increase in out-of-pocket requirements for patients, even in tax-financed health care systems such as the one in Belgium⁸⁷. If national health services are to cover the expenses for xenotransplantation, such a decision must invariably involve a trade-off with other health care options.

In our justification of allocating health care funding to allotransplantation, we applied the maximin principle, as well as the principle of maximized net social utility. However, in questioning whether those justifications can be generalized to legitimize xenotransplant funding, some critical notes are in place.

Maximin. The first approach is based on the principle that health care resources should be distributed so as to enhance greater health equality among all citizens. If choices must be made, a more substantial share of the resources should be distributed to the worst-off in terms of health care needs. What constitutes a health care need is a matter of debate, but

Daniels has delineated the concept in light of the normal range of opportunities an individual would have were he or she in good health⁸⁸. An individual's 'normal range' is dependent on normal species functioning, his or her specific skills and talents and the level of societal material wealth and historical/technological development. A normal range of opportunities would allow the individual, were he or she in good health, to pursue reasonable, happiness-producing life plans and conceptions of the good. In general, the disease conditions that involve a greater reduction of an individual's share of the normal opportunity range, should receive priority in health care allocation.

Given the impact of end stage organ failure on an individual's share of opportunities, a life-saving xenotransplant would obviously count as meeting a health care need. Some cellular nonvital xenotreatments will also be relevant in this respect, in their ability to alleviate chronic disabling limitations on activity. Nonetheless, from the normal opportunity-range perspective, not all xenotransplants will be considered equally important. In particular, the claim for a fair share of the range of normal opportunities does not always apply for all age groups. The latter argument is often used to criticize health care that primarily targets elderly patient populations. Note in this respect that, according to studies in OECD countries, patients aged 65 and above consume four times more health care than those aged under 65⁸⁹. Daniels asserts that procedures meant to delay the effects of normal aging do not address a real need, since normal aging does not deviate from normal species functioning⁹⁰. Callahan, too, limits health care to those treatments that are directed toward improving the quality of life within a finite life cycle and to conquering those diseases and conditions that bring a premature death⁹¹. In this respect, xenotransplants for nonvital complications that arise as a result of an aging population, such as neural xenotransplantation for neurodegenerative disease, will be most difficult to justify. And although kidney transplantation offers a lengthening of an average of up to 5 good quality years of life and proper graft survival for patients even older than 75 years⁹², expenditures on solid organ xenotransplantation will not be legitimized if they target that age group only, or predominantly. Such treatments could be called disease care rather than health care.

Proposals to ration health care for the elderly are not uncontroversial (and often labelled 'ageist'), particularly within societies that demand increasing productivity from their aging populations. Nonetheless, if age, in light of claims on life-plan opportunities, can be considered a relevant moral criterion to ration choices, that would not eliminate the appeal for xenotransplantation entirely. It would merely support the existing trend to

prioritize transplanting younger patients and patients with dependants. Waiting list statistics clarify that all age groups require, to a varying degree, vital organ replacement therapies. Of the 98,471 patients currently on the national US waiting list for an organ, an average of 13 per cent (12,980) is aged 65 or more⁹³. However, roughly 2 per cent (2,215) of the patients on the waiting list is aged 0 to 17, and 11 per cent (11,116) is aged 18 to 34. Furthermore, although only 1 death is reported on the 2005 Eurotransplant waiting list for kidneys among patients aged 0 to 15, the highest mortality rates are among the age group 16 to 55 (41 per cent of the 565 deaths)⁹⁴. That age group also accounted for the highest death rates among patients awaiting a heart (49.8 per cent), a lung (60.7 per cent), a liver (53.3 per cent) and a pancreas (94 per cent) transplant⁹⁵. If we are to focus health care on patients with the least access to a normal opportunity range, the impact of end stage organ failure on children and adults in their prime clearly makes way for a high priority claim. This is all the more compelling in light of the fact that it is most difficult to find appropriate replacements for certain organs, such as the heart, for very young infants. The pigs bred as source animals may provide organs that are of suitable size. Islet cell xenotransplants could also address the health care needs of an ever-growing population of young patients afflicted with chronic diabetes.

Still, it remains highly debatable whether a focus on those who are most in need of a transplant will accommodate the *overall neediest* of patients. Daniels has questioned whether cardiac transplantation should be funded, given that many other options might be more effective and efficient in protecting the normal opportunity range for a larger group of patients⁹⁶. Oregon has led the way in rationing transplants on the basis of such considerations. In 1987, the state legislature decided to stop solid organ transplant coverage from Medicaid, the US programme that covers certain medical expenses for low-income individuals and families⁹⁷. It was determined that cutting expenditure on transplants would better meet the needs of the least well-off by reducing infant mortality through greater investments in prenatal maternal care.

Maximized utility. Although it could be argued that programs which specifically reduce infant mortality must be granted priority over increased expenditure on the field of transplantation, we have also supported the allocation of health care resources to allotransplantation in terms of maximized pay-off to society. As we saw in Chapter 1, in developed regions, the proportion of people with chronic diseases potentially treatable by transplantation - such as cardiovascular disease, cancer and diabetes - is enormous and is expected to grow. Furthermore, allotransplantation of solid organs often provides the best

overall anticipated health gains at lower costs in comparison with non-transplantation or alternative treatments. Further societal savings may also result from post-transplant re-employment. Nonetheless, here too, some additional conditions for justifications of xenotransplant funding must be noted.

For one, it is ambiguous whether the prospect of re-employment is a valid justification of transplant costs. In a review of post-allotransplant employment, Paris *et al* indicate that fewer than 50 per cent of organ transplant recipients who are clinically judged physically able to work, actually return to successful employment⁹⁸. Post-transplant depression and anxiety rates, which are reported above 50 per cent, appear as important factors that decrease the patient's capacity to function optimally in a work environment. It is possible that such psychological complications will increase after an organ xenotransplant, at least in the early years (see Chapter 9).

The net health gains of allotransplantation are also not left uncontested. Fox and Swazey have critiqued an over-utilization of transplantation as an often zealous effort to save life at any cost⁹⁹. Their concern is related to the over-glorification of the quality and quantity of life that may follow and the use of these procedures for patients whose overall health status is severely compromised. That observation again brings to light the difficulties of justifying xenotransplantation if it does not establish substantial benefits in terms of high-quality life years gained.

Furthermore, while in many cases allotransplantation of solid organs is more cost-effective than dialysis or conventional treatments, it is in no way clear that the same will be true for xenotransplantation. The ongoing costs of post-transplant care constitute the limiting factor of allotransplant cost-effectiveness against other existing treatment options¹⁰⁰. If xenotransplantation, as mentioned above, requires more aggressive and expensive immunosuppression, the investment in follow-up will be even greater. Of course, the demand for such therapies could be reduced given that some patient populations, such as the elderly, may not be able to tolerate the toxic effects of immunosuppression. Cellular therapeutic modalities that do not require long-term immunosuppression are more attractive in this respect. If adequate graft function and survival can be obtained, cellular grafts could, in principle, provide cell therapies that are cheaper and less invasive alternatives to whole organ transplants.

In the long run, it will also be essential in terms of cost-effectiveness to prove that xenotransplantation is a better use of resources than alternatives currently still under development. Given that the costs and outcomes of regenerative medicine or artificial replacement technology are not fully known, a comparative analysis is purely speculative at this stage. There is, however, one alternative, which is often regarded as being by far the best way to maximize societal pay-off. Effective prevention would undoubtedly lead to greater net health benefits than the large-scale administering of replacement medicine¹⁰¹. Cardiovascular disease, cancer, chronic lung diseases and diabetes mellitus are for a great part induced by tobacco and alcohol use, unhealthy diets and lack of physical activity¹⁰². Increased focus on preventive care could reduce the future burdens of exposure to those risk factors and that would be the most effective and efficient way to raise overall health levels at lower costs¹⁰³. Ideally, the emergence of new, curative biomedical technologies should not drain public resources from such prevention measures. However, graft-engineering procedures emerge as a possibility for those patients who require treatment before the effects of prevention measures may become tangible and to those who develop congenitally acquired pathologies.

Allocation problems are inescapable in areas of modern medicine and there can be no uniform answer to the question whether the expected benefits of an emerging technology must be granted a priority in health care funding. Unfortunately, we cannot provide a more comprehensive analysis of the resource implications of xenotransplantation. That would require a lot of additional information regarding comparative costs and outcomes, much of which is still a matter of speculation. What is clear, however, is that cost will play a major role in determining whether widespread implementation of clinical xenotransplantation will occur or not. In the end, it is reasonable to expect that the decision should lie in the authority of the public, who will (indirectly) bear the costs. Currently, however, there is reason to be sceptical about the favourable attitude of the public in this regard. In Canada, an extensive public consultation on xenotransplantation was conducted, consisting of citizen forums and mail-in/telephone/website surveys. Among the results of that consultation, only 30 per cent of the forum, 35 per cent of the mail-in, 22 per cent of the website and 35 per cent of the telephone survey respondents supported a redirection of health care resources to xenotransplantation¹⁰⁴. The main objections were based on scarce funds, high costs and other health care priorities.

Of course, it can be expected that such opinions will shift the more the science base of the technology progresses. Indeed, we believe that in light of the considerations above, there

are various conditions under which justifications of allocating health care funds to future xenotransplantation applications will be most compelling. That will be the case if xenotransplantation provides more than merely a bridge to allotransplantation: it should optimize the outlook of substantial benefits in terms of high-quality life-years gained and primarily be attributed to patients for whom such an outlook is realistic. It should also provide an appropriate replacement therapy for children. Furthermore, the cost-effectiveness of xenotransplantation is for a great deal dependent on the level of immunosuppression required. The use of effective cellular therapies will be most advantageous in that respect, particularly if the costs are minimized through efficient use of adult source animals and maximized procurement from foetal animals. Further pre-clinical research in xenogeneic infectiveness may also alleviate some of the follow-up costs.

11.3 Pursuing xenotransplant research: time to bring home the bacon?

We highlighted the importance of persistent and extensive research in pig-to-human infectiveness, immunology and physiology before xenotransplantation can proceed to the clinic. At this point, the benefits do not outweigh the risks to the public and the patient. The most pressing condition for a favourable risk/benefit analysis is further identification and exclusion of the infection or recombination potential of detectable organisms. Clinical trials involving solid organs, particularly, also still await major advances in countering immunological and physiological incompatibilities before prospective recipients can reasonably expect a substantial longevity and quality of life. Although such an expectation may be a rather high standard for an experimental therapy, it is nonetheless crucial in order to counterbalance inevitable levels of ‘unknown’ risk to the patient and to enhance public acceptance. It will also be important in order for the procedure to make a compelling claim on public health care funding and to produce a positive rather than a negative effect on the waiting list burden.

While further reducing the risks of xenotransplantation is obviously in the best interests of patients and public, however, it implies an *increasing* harm to the research animals. It also implies an additional and substantial channelling of time and financial/infrastructural resources. Industry estimates indicate that the development and marketing of most new drugs or biological products take an average of 10 to 12 years¹⁰⁵. The development of transplantable xenogeneic organs has already far exceeded this time frame, with

experiments sporadically attempted over the past *century*. Despite that long time span, there have not yet been major medical breakthroughs and it remains uncertain whether the research will eventually pay off in successful, clinical applications of the type we have identified. Given the uncertainty of outcome, it is worth questioning under what conditions it is justified to continue to invest these resources in xenotransplant research.

‘Potential’ benefit versus direct losses

Surely all biomedical research requires considerable financial and infrastructural means. It remains unclear what the proportion of xenotransplantation research is to average investments in those terms. However, the need to justify continued support for xenotransplantation research is perhaps pivotal when considering that it requires an enormous level of ‘investment’ in terms of animal lives. Thus far, we have justified the use of pigs as source animals in reference to the direct benefits that accrue to humans. Such a *direct* comparative assessment does not apply for the animals that have already been and will continue to be sacrificed during the long and uncertain stages of research. The harms done to those animals can only be weighed against a continuously postponed prospect of benefit.

We have not addressed ethical issues regarding the use of animals for xenotransplant research in depth because it is not a unique concern for xenotransplantation, but rather an ethical problem inherent in most types of biomedical research. Specific aspects of xenotransplant research nonetheless indicate that there may be more at stake here than in other research areas. In particular, xenotransplant research is distinctive in terms of the proportion of animals used and the level of suffering implied by the research. Animals are used both as research models and as sources of the grafts that are to be tested in those models. The proportion of animals used will thus exceed that of research that uses animals only in the first sense. The research area is also inherently dependent on the use of nonhuman primates (mostly monkeys and baboons) as surrogate models in order to best extrapolate human responses to porcine immunology and physiology. In light of our capacity-dignity arguments, the use of primates for research purposes is a particularly sensitive spot in our assessment of the ethical acceptability of xenotransplantation.

Given that xenotransplantation research programs are running in countless institutions worldwide, we cannot provide an estimate of the total number of animals (in large and small animal models) sacrificed to date. As a general statement, we cannot help but feel

frustrated by the lack of transparency of such information. The little data available reveal that, by 2001, up to 10,000 pigs had been killed for xenotransplant research purposes in the UK alone¹⁰⁶. According to statistics cited by Schicktanz, during the 1990s, the UK and Germany (which, together with France, are by far the largest investors of primate lives for research in Europe¹⁰⁷) used 3,500 and between 1,500 and 2,000 nonhuman primates, respectively, for research every year¹⁰⁸. In Germany, between 1999 and 2000, 2 to 5 per cent of those animals were specifically used for xenotransplantation purposes. In the UK, that proportion is larger. By 1999, researchers at Imutran (a subsidiary of the multinational drug firm Novartis Pharma, which produced the first transgenic pig) had conducted more than 350 porcine organ transplants in primates¹⁰⁹. That amounts to at least 10 per cent of this nation's research involving primates.

As indicated above, our defence of the use of willed body donation in case of a PVS also applies as a response to concerns over the interests of primates. However, we understand that this is, on a societal level, a controversial step and that general acceptance is not within reach. Even if it were, it could take many years before PVS bodies with prior consent are available. The mechanisms for requesting and registering such a consent must first be put in place and the procedure must be made known to the general public. A perhaps more practicable scenario would be the use of whole brain dead bodies, which has also been suggested as a model to study the effects of xenografts on human immune and complement systems. According to Thomas Starzl, even if we could observe the effects of such xenografts for only a few hours, the pathology study would provide more valuable information than any animal models¹¹⁰.

Undoubtedly, for some people, the need to use higher primates for xenotransplantation research is reason enough to oppose it on the whole. We realize that a fundamental consideration of the interests of primates should necessarily lead us to object to all research involving their use. In that respect, it is interesting to note that, as suggested by the above percentages, xenotransplant research programs are not the major consumers of primate lives. Conlee *et al.* indicate that in the US, which uses up to five times more primates than the European Union (approximately 58,000 versus 11,000), the research focus lies on hepatitis viruses, cognition, behavioural and HIV research¹¹¹. An extensive review of studies published in peer-reviewed journals in 2001 reveals similar results: the most common areas of primate research involve microbiology (including HIV/AIDS research), neuroscience, biochemistry and pharmacology/physiology¹¹².

Most people will accept that the use of even primate models for certain types of biomedical research is a 'necessary evil' for the greater good. What is important in justifying their use, then, is that all is done to minimize the 'necessary evil' as much as possible. That relates to the need to conduct the research in accordance with the ethical standards that the number of animals used is absolutely essential to contribute to progress in the research field, that the animals are used only for lack of alternative models and that they are afflicted with the least possible level of suffering or pain. Compliance to such standards evidently is a first condition for further investment in xenotransplant research and the importance thereof has been addressed since the early advisory reports on xenotransplantation¹¹³.

Nonetheless, there are some reasons as to why the use of primates is an especially sensitive issue for xenotransplantation research. For one, past experiments have been conducted in direct breach of legal limits on animal suffering. As was briefly mentioned in Chapter 6, Dan Lyons of Uncaged Campaigns published a report entitled *Diaries of Despair: The secret history of pig-to-primate organ transplant experiments*¹¹⁴. The report is mainly based on correspondence between the above-mentioned biotech company Imutran, Huntingdon Life Sciences (an affiliate Contract Research Organisation) and the UK Home Office. The confidential documents leaked in the spring of 2000 from an anonymous source. They included study reports that detailed the procedures and results of genetically modified porcine organ transplants into the necks, abdomens and chests of hundreds of cynomolgus monkeys and baboons. It was shown that more primates were killed than declared and that some of the primates were wild-caught. The duration of shipment of imported primates was longer than the time approved by the Home Office. The cages used also violated size and ventilation regulations. In various experiments, furthermore, the transplant procedures failed due to avoidable technical mistakes. For instance, several primates were overdosed with anaesthetics, one monkey was accidentally transplanted a frozen pig kidney and another monkey died from a lethal infection due to a swab that was not removed from the abdomen after surgery¹¹⁵. Lyons has published a letter in *Nature*, in which he accuses the UK government animal research authorities of serious malpractice¹¹⁶.

Of course it would be wrong to stigmatize all xenotransplant research on the basis of this particular case of non-adherence to ethical standards of animal research. Nonetheless, even if we can assume that xenotransplant researchers generally do all that is required to minimize the necessary evil, many xenotransplant experiments inevitably involve a greater level of harm than general research objectives. While other programs may require a larger

investment of primate lives, xenotransplant primate models often involve major transplant surgery which - apart from the adverse effects that may arise by mishap - can cause painful recovery, organ rejection and/or failure, infections and complications from aggressive immunosuppression regimens. As such, it constitutes a significant proportion of the few research programs that require invasive research (2 per cent of the studies published in 2001¹¹⁷).

In light of these considerations, the burden of the investment that is at stake should not be underestimated. Therefore, however much we depend on progress in pre-clinical research before we can reach a point at which it is justified to proceed to the clinic, the credit to continued xenotransplant research programs cannot be unconditional.

Potential benefit and the Concorde Fallacy¹¹⁸

The Concorde is widely known as the most expensive and at once most disappointing marketing experiment in history. The supersonic commercial aircraft took over twenty years of engineering and testing before regular commercial flights were conducted. Although the aircrafts were not lucrative, the British and French governments long continued their investments in the project. That decision was based on the belief that ending the project would mean a waste of the considerable amounts of money already invested.

With the benefit of hindsight, we can certainly recognize the impact of the flawed reasoning in this historical example. The dedication to past investments was an irrational factor in the decision to pursue the project and resulted in a dramatic waste of public resources without any significant recovery of the prior investment. Nonetheless, it is worth mentioning that *during* the process of decision-making about commitment to a future investment, we are often intuitively liable to committing that fallacy. An example often given in this regard is the imaginary scenario in which you pay for a movie ticket in advance and come to regret your purchase, perhaps because you know you will not like the movie or there are other activities that you would prefer. In such a case, many people would still consider it a waste not to use the purchased ticket. However, that decision would be irrational. If you decide to use the ticket, the money is wasted anyhow, as it could have been better spent otherwise. In addition, deciding to see the movie is an additional investment of time that could be valuable for other activities and thereby produces an overall greater 'waste'.

At the very least, the example points out that the investment of money, time and animal lives thus far should play no role in deciding whether or not to continue xenotransplantation research. Neither should the enormous level of energy that has been devoted to the international development of xenozoonosis risk regulations and surveillance systems. If the research does not appear to be ‘lucrative’, in the sense of attaining the substantial benefits we have identified, pursuing prior investments despite that would consist in committing the Concorde Fallacy.

Of course, the slow progress to clinical success does not in itself negate the possibility that xenotransplantation will attain the potential benefits at some point in time. Science attempts to discover what is unknown, and as such, the results are inherently unpredictable. The research required to resolve the issues of successful xenotransplantation are even more complex than those encountered in the development of allotransplantation, which also breached the above mentioned average time to development and marketing of new drugs or biological products considerably. In fact, further research in allotransplant immunology is still required, in want of better long-term outcomes. While it is inherently flawed to benchmark a research area based on time to success, indications that we are well on the way of attaining success, however slow we walk the steep tracks, are nonetheless essential.

In light of the actual achievements to date, as detailed in Chapters 4 and 8, it is highly debatable whether we can interpret the progress in xenotransplantation favourably in those terms. Ringe *et al* quote Thomas Starzl to support a justification of pursuing progress:

“the future of xenotransplantation is brighter than at any previous time because what must be done to succeed has become remarkably clear.”¹¹⁹

While that may be the case, it is in no way clear that what must be done *can* be done. The optimism dates from the time in which there was unbound enthusiasm regarding the advances in the genetic manipulation of pigs to avoid hyperacute rejection. That enthusiasm led researchers to predict, as early as 1995, that clinical solid organ xenotransplants would be conducted within 5 years time. In 1996, Peter Laing predicted that pig-to-human kidney transplants would become possible by the year 2000 and that the market could reach \$6 billion by 2010¹²⁰. Laing was a pharmaceutical analyst and studied the business potential of xenotransplantation for Sandoz, a major manufacturer of

immunosuppressive drugs and at that time part owner of commercial rights to Imutran's technology for the production of transgenic pigs. Clearly, the feasibility of organ xenotransplantation has been seriously overestimated. Some researchers even misled objective assessments of the level of pre-clinical progress. Here too, Imutran has played a particularly unfortunate role for the reputation of xenotransplantation research. According to the Daily Express, the leaked Imutran-Home Office documents reveal that Imutran researchers deceitfully published the results of their longest surviving pig-to-baboon cardiac xenotransplant recipient¹²¹. The results were published in the *Journal of Heart and Lung Transplantation* in 2000. A baboon is reported to have survived for 39 days, which the authors identify as "significant progress in the development of a viable strategy for clinical xenotransplantation"¹²². The animal is said to have been active and energetic throughout that period, showing no signs of cardiopulmonary failure. According to the Express, however, Imutran's log demonstrates that this particular baboon suffered a severe debilitation of its condition following the transplant. It also shows that the pig heart had grown to three times its weight by the time the baboon was killed.

Contra-evidence of progress in improving survival rates may be concealed as a strategy to maintain private investments. Indeed, the many challenges that have hindered clinical success have made it very difficult for xenotransplant research programs to safeguard the high level of industry funding that was gained during the 1990s. The private funding was primarily awarded to institutes - such as Imutran, Nextran, Alexion, BioTransplant and PPL Therapeutics - that were dedicated to overcoming hyperacute rejection by genetic modifications¹²³. By 2004, those biotech companies - as well as others, such as Circe, Diacrin and Immerge - effectively withdrew from the field, reorganized their business alliance or greatly reduced their interest in xenotransplantation¹²⁴.

It is clear that overcoming hyperacute rejection only to gradually discover subsequent processes of rejection and physiological incompatibilities does not furnish short-term pay-offs. Before xenotransplantation can attain substantial improvement in survival rates, the remaining immunological barriers must be conquered and it remains highly uncertain whether that is possible. Cellular xenotransplants are advantageous in this respect. For lack of vasculature, cells have reduced immunogenicity. Notwithstanding our criticism of the recent clinical trials involving porcine islet xenotransplantation, the two recent reports of more than six months of insulin dependence in pig-to-monkey transplants (as mentioned in Chapter 8) provide promising indications of feasibility of this procedure^{125,126}. Moreover, while it remains speculative to date to claim that solid organ xenotransplantation can

overcome the remaining immunological barriers, we have not yet reached the point at which it appears we have gone astray in this research area either. At least for cardiac and kidney xenotransplantation (which involve much less complex organs in comparison with lung and liver xenotransplantation), there have been ongoing, albeit modest increases of survival rates in pre-clinical models. At the last conference of the International Xenotransplantation Association, Byrne *et al.* reported life-supporting transgenic pig-to-primate cardiac xenotransplantation in two primates surviving 5 to 8 weeks¹²⁷. The maximum survival implies a prolongation of 17 days when compared to the 39-day survival reported by Imutran in 2000. In Chapter 4, we noted that pre-clinical experiments involving the use of GALT-KO kidneys showed prolongation of maximum survival when compared to the maximum survival of transgenic renal xenografts (83 days¹²⁸ compared to 78 days¹²⁹). While the increase of survival in number of days is perhaps not very significant, the course of the graft function is. The study involving GALT-KO kidney transplants was combined with a protocol directed towards tolerance induction: primates received porcine thymic tissue (part of the immune system which generates T-cells) along with the GALT-KO kidneys. The three control animals only received immunosuppression and rejected the GALT-KO kidneys after 20, 33 and 34 days. Of the non-control group, a distinction in survival rates can be made based on the particular regimen of tolerance induction used. Three assessable recipients had received vascularized thymic lobes and survived for 31, 56 and 68 days. Two other assessable recipients had received thymokidneys (kidneys with vascularized donor thymic tissue under their capsule) and both survived more than 80 days. Significantly, all five recipients of either tolerance protocol showed *normal* functioning of the xenograft and no rejection until time of death. If we can accept that the results of such recent experiments are not exaggerated, they offer proof of ongoing progress.

Potential benefit and research priorities

Even if incremental progress in xenotransplantation research persists, however, there is a last condition that we feel is relevant in determining continued dedication to this field. That condition is dependent on whether or not there are better options in which to invest the research resources.

As evident from the review in Chapter 3, there are other technological research options that are equally dedicated to the potential benefits of xenotransplantation. In particular, artificial organs are being developed to provide permanent and quality-of-life-enhancing surrogates for organ failure. Whereas that technology is limited in scope in comparison

with the wide range of diseases which cellular xenotransplantation could potentially treat, stem cell research and tissue engineering promise to support or replace virtually any graft functions.

At the moment, it is not clear whether those technological alternatives are ‘better’ research options. Mechanical organ substitutes and regenerative medicine are also still left wanting of results that indicate the feasibility of providing a substantial pool of durable, transplantable grafts in the near future. Ideally, in order to enhance quality of life, mechanical substitutes would be totally implantable for patients of all sizes. Such approaches are lacking for liver replacement. For kidney, heart and lungs, implantable devices have not been optimized and there are still important challenges in establishing mechanical support or replacement as a destination therapy. The major problems currently restricting the use of adult and embryonic stem cells relate to the possible rudderless differentiation of the cells and the risk of forming unwanted tissues and tumours (however, the latter risk applies to organ and tissue xenotransplantation as well). In addition, the use of stem cells currently does not allow for the reproduction of the complex micro-anatomical structures and functions of multi-tissue organ structures. Gene therapy - which we did not discuss in our review of alternatives to human graft donation - may provide viable treatment for (and prevention of) virtually all diseases that have a genetic origin through replacement or repair of the defective genes. However, although interest in this field is re-emerging, it is generally accepted that the use of gene therapy to annul symptoms of organ failure is in an even more primitive stage of development than the other alternatives. Moreover, many hereditary diseases that may benefit from a transplantation, such as heart disease, Alzheimer’s disease and diabetes, are caused by an interaction between various genes.

Given the problems in the development of those alternatives, we illustrated why it is generally assumed that xenotransplantation stands closest to providing an overall solution to the human graft shortage. However, in retrospect, and again apart from the recent progress in islet xenotransplantation research, it is insufficiently substantiated to claim that this will necessarily prove to be the case. Even regardless of the need to further exclude the infection risk, the slow progress in attaining sufficient pre-clinical xenograft survival does not render it impossible that alternative research programs will eventually progress at a faster pace. Pre-clinical and clinical results of mechanical heart assist devices are still superior to those obtained with xenografts in nonhuman primates¹³⁰. Apart from the more common bone marrow and peripheral blood stem cells transplants, the use

of adult stem cells for various treatments is rapidly moving forward, most notably for cardiac repair¹³¹. The recent report of limited experience in transplanting engineered autologous bladder tissues¹³² has also brought progress in regenerative medicine to the foreground. Admittedly, generating complex, vital organs will prove to be much more complex and that particular breakthrough does not warrant proof that regenerative medicine is a nearby solution of the organ shortage either. In fact, as we saw in Chapter 3, a new, commencing line of research involves a combination of regenerative medicine and xenotransplantation. It remains to be seen which of those alternatives, or which combined form, will develop to be the nearest safe option for the various conditions we have considered.

However, there is reason to argue that it is merely the anticipation that xenotransplantation is the most *imminent* solution that currently justifies rational decisions to pursue that particular research field. If the alternative technologies, or certain procedures, were to gain substantial indications of feasibility, continued dedication to research of the equivalent xenotransplant procedures would be difficult to justify. The research into those alternatives requires less investment of animal lives. Particularly in the field of artificial organs, animals are only used as experimental recipients, not as sources of the products that are to be tested. In that research area, considerable advances have also been made to allow for the physical testing of mechanical performance of the devices under realistic conditions through computer simulations rather than animal models. As such, continued pursuit of xenotransplantation would go against a generalized norm to minimize the number of animals used to attain a research goal. It is also reasonable to expect that the overall risks, costs and harms of implementing those alternatives in the clinic will be less than those involved in xenotransplantation. The production of the alternative graft replacements is not inherently dependent on the use of animals. Furthermore, the alternatives do not bear a risk of harming public health (unless regenerative medicine involves the use of stem cells that are exposed to living animal-derived material and unless gene therapy uses unqualified viruses as vectors for the replacement genes). The major risks involved in regenerative medicine and artificial replacement technology only apply to the patients. Not only do these conditions thereby minimize potential dangers for public and patients by comparison with xenotransplantation, they also annul many of the costs related to graft screening and blood and tissue archives. Regenerative medicine has the additional advantage that the recipient's own cells can be used to generate replacement tissue, thereby avoiding the

problem of immunological rejection altogether and avoiding the long-term complications that limit the current acceptability of allotransplantation.

In short, it appears to be of paramount importance that future investments in xenotransplantation are reviewed at regular intervals for indications that the various procedures can obtain the potential benefits *sooner* than other research developments. While xenotransplantation has not yet been outstripped in those terms, it is important to note that there is at least a theoretical possibility that future commitment to xenotransplantation research threatens to boycott a 'fair race'. As a result of decreased industry funding, ongoing xenotransplant laboratory research has become increasingly dependent on federal funding. According to Leonard Bailey - the surgeon who conducted the xenotransplant on Baby Fae - the field is now almost *exclusively* supported by grantsmanship¹³³. Increased government interference has the advantage of enhancing reliable information regarding the true rate of progress, rather than when knowledge is a privately owned commodity. However, as is the case for public health care funds, federal resources for research are limited and inevitably require some form of trade-off between competing claims for funds. It is possible that the need for further research in the field of xenotransplantation will divert resources from the development of those alternatives. From the few indications of research fund allocations we have, that does not appear to be the case currently. Although federal funding for the creation of embryonic stem cell research was until recently prohibited in the US, \$3 *billion* is currently devoted to this research field in California alone. By comparison, according to an educated guess by Daniel Salomon¹³⁴, the US National Institute of Health spends a 'mere' total of \$25 million for xenotransplantation research. Unfortunately, this kind of information is extremely difficult to obtain for European nations.

The comment is nonetheless useful to demonstrate the need for a continued and careful analysis of what our research priorities are and what the effect of that priority-setting will be on the development of overall least costly (and we use this term in its most broad sense) health care options.

To do nothing, or to prevent others from doing anything, is itself a type of experiment, for the prevention of experimentation is tantamount to the assumption of responsibility for an experiment different from the one proposed.¹³⁵

The reader may recognize this quote from the beginning of the fourth chapter. It served there to illustrate the critique on ethical and regulatory restrictions to clinical trials of

xenotransplantation. However, in this context, the quote can be read quite differently. There *is* responsibility for experiments different from the one proposed, and it is of crucial importance that we do not lose sight of that responsibility by uncritical expectations that xenotransplantation is just over the horizon.

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APPENDICES

1 LEVY N. Respecting rights... to death

Perhaps the single most important advance in moral thought occurred when it came to be generally recognized that all persons are protected by rights that are inviolable. The precise nature and content of these rights is controversial, but there is a consensus among reasonable people over their core. We all have a right to life, to liberty, to security of person and to equality before the law. Other rights - so-called positive rights, such as the right to economic security, or economic and cultural rights, for instance - may be controversial, but we all agree at least on these.

Ravelingien *et al.* therefore seem to be on solid ground when they conclude that it would be impermissible to use living persons as subjects in clinical trials of xenotransplantation, since such trials would potentially or actually, result in the violation of the core human rights of the subjects. The argument proceeds as follows: Xenotransplantation carries with it a currently unquantifiable risk of resulting in the transmission of viruses from the animal that is the source of the organ transplanted to the human recipient. Such viruses could have potentially catastrophic consequences, including triggering a global and devastating pandemic. Therefore, it would be necessary to monitor the health of recipients of donated organs for many years, even decades, to ensure that the symptoms of such infection have not developed. The recipient of such a transplant would therefore need to submit to a regime of intensive and extensive scrutiny. They would have to make themselves available for regular testing and their sexual partners would have to be warned of the potential for infection. They might be advised to forgo having children. Worst of all, if signs of an infection are detected, or if the risks are felt to be great enough, they might find themselves confined in quarantine. But all of these actions are violations of their human rights. Since we have a right to shape our life as we see fit, to associate with whom we like and to travel where we like, we cannot morally be treated in the ways that xenotransplantation on persons would necessitate.

Ravelingien *et al.* therefore suggest that xenotransplantation trials should be conducted only on people who are in a persistent vegetative state. Since such people no longer have an interest in freedom of movement and association, we do not violate their rights by confining them. If they had, when competent, consented to participate in such trials, using their bodies for clinical trials of xenotransplantation should be no more controversial than

the range of uses to which we currently put cadavers in research and in the training of surgeons.

However, this proposal faces a serious objection. If it is permissible to use PVS patients in clinical trials of xenotransplantation (and I think it is, if all safety considerations can be successfully dealt with), then why isn't it permissible to give such transplants to patients who would otherwise die? Using terminally ill patients, rather than PVS patients, has several advantages. First, it is conceivably the case that any virus transmitted from animal donors to human recipients could produce effects in normal persons, but none in PVS patients. This would be the case, most obviously, if the virus attacked those parts of the brain which are irretrievably damaged in PVS patients, such as the cortices, while leaving the brain stem unaffected. To that extent, a competent agent would be a better subject for clinical trials than a PVS patient. Second, terminally ill patients could potentially benefit from xenotransplantation, by receiving a more or less lengthy extension of their lives as a result of participation in the trial. For the same reasons that PVS patients cannot be harmed by the restrictions the trials would require, they cannot be benefited either. Conversely, for the same reasons that the terminally ill could (potentially) be harmed by these restrictions, they can be benefited.

Ravelingien *et al.* argue that we cannot ethically place such restrictions on people who have done nothing to deserve them. This seems to me false. Though we are prohibited from violating the rights of others, anyone is entitled - has a *right to* - waive their rights. If patients can only avoid death at the cost of sacrificing some or all of their rights to freedom of movement or association, then they have a right to make this choice, and - on the assumption that no one is responsible for the predicament that forces them to choose between these options - no one has acted unethically. To see this, consider the absurd consequences that might follow if the proposal advocated by Ravelingien *et al.* were to be implemented. A patient suffering from a terminal illness might volunteer to participate in potentially life-saving xenotransplantation clinical trials. The scientists conducting these trials would be forced to respond: "we cannot use you now; make a living will and perhaps we shall consider you once you die". The patient is assured that her rights will be respected, but this seems to me small comfort.

Of course, as Ravelingien *et al.* point out, patients who consent to the restrictions envisaged as a condition of participating in clinical trials might change their minds after receiving the transplant. We should have to be prepared to continue to restrict their

movement, even against their wishes. I do not see this as a great worry. If there is a real public health risk, then we would have to be prepared to restrict their movement in any case, whether or not they had consented to participate in the trials. We already possess the right and the responsibility to protect public health, even at the cost of infringing rights: carriers of infectious diseases can already be quarantined against their wishes. The fact that recipients had agreed to participate in the trials simply makes our decision easier. There is, therefore, no ethical barrier to using the terminally ill in xenotransplantation trials.

2 CURRY S. Living PVS patients as legitimate research subjects: a response to Ravelingien *et al.*

An Ravelingien and her co-authors argue that we should re-categorize people in Permanent Vegetative States as dead.¹ While the dilemma they describe is very real, their solution will not work. Other respondents to this paper have advanced several powerful arguments against the attempt to describe PVS patients as dead. Fortunately, the original argument contains sufficient resources to develop an alternative solution to this dilemma, without having to radically alter the current legal or social status of PVS patients. In fact, living PVS patients may be enrolled in xenotransplantation experiments, provided that their prior informed consent has been sought.

The motivation for the original paper is to resolve an apparently intractable ethical conflict. On the one side are powerful ethical and medical reasons for proceeding with research into the transplantation of non-human organs into human patients. On the other side are equally powerful ethical reasons for blocking whole organ transplant experiments. These reasons are unusual in that special problems with xenotransplantation will block experiments that are permitted in other cases. In particular, the unquantifiable risk of a pandemic triggered by diseases such as porcine endogenous retrovirus crossing the species barrier will either block the research or expose subjects to the risk of indefinite quarantine (p.93). The authors also argue that the restrictions placed on transplant recipients and the possibility of long term and intrusive monitoring, restrictions on sexual contacts and reproduction, and possible confinement represent excessive and ethically unjustifiable burdens. Over time the recipients may wish to withdraw their consent, but the risks to public health would prevent them doing so, thereby violating the basic principle that subjects of scientific and medical experiments should be able to revise or withdraw consent (pp93-4). So-called “plural consent” would also have to be sought from a wide circle of family and social contacts. These considerations frame a substantial dilemma that could be solved by using PVS bodies for initial research. The authors have tried to cut this

¹ A. Ravelingien, F. Mortier, E. Mortier, I. Kerremans, and J. Braeckman “Proceeding with clinical trials of animal to human organ transplantation: a way out of the dilemma”, *Journal of Medical Ethics*, 2004: 30; 92-98.

Gordian knot of competing ethical considerations by placing PVS patients in the same ethical category as cadavers.

I will not repeat the arguments against this strategy. Others have argued persuasively that the conceptual shift necessary to achieve this re-definition of death will either fail on the evidence, fail conceptually, or will founder on its consequences. However there is no need to make the attempt. All that must be achieved is to overcome the ethical objections that block experiments on “normal” subjects. We can cut the knot from a different direction, by showing that PVS patients are - in exactly the right kinds of ways - not like other patients, whether or not they are dead.

Consider the reasons why the authors think xenotransplantation trials would be impermissible with living subjects. None of these concerns apply to PVS subjects. Bear in mind that our problem is that it would be wrong to impose these various burdens on normal subjects even if they consented. The issue is not one of consent, but of the interests that are stake. We commonly think that some interests are so foundational to human welfare that they cannot even voluntarily be given up. If a subject did not have these particular interests, and had given appropriate informed consent, the ethical problems would evaporate. It just so happens that PVS patients do not have any of the interests listed by the authors. Persons who are in PVS will not ever wake up, they feel no pain or discomfort, and have no continuing interest in their own survival. Even if one thinks that PVS patients have a right to life (on even the most contentious meaning of this term), these patients must also have a right to risk that life for the common good. Since they have no other interests to risk, their decision to risk their lives in transplantation research is ethically unproblematic. The subjects will not be able to have children, and have no capacity for movement, so that their possible confinement does not violate the interest that underpins the right to free movement. Similarly, since they will have no more sexual contacts, nor any uncontrolled social contacts, the issue of plural consent is irrelevant. There is also no risk of withdrawal of consent.

Consent must still be sought from the subjects. The authors suggest that if PVS subjects are classified as dead, prior consent should be sought by asking the public to include their consent in testaments, as well as enrolling on a whole body donation register. The exact same technique could be used if PVS patients are thought to be alive. Willingness to be enrolled in trials could be communicated by opening an annexe to the whole body donation register, intended for living subjects. The registrar could distribute literature to intending

registrants to ensure that their prior consent is fully informed. In this way PVS subjects could be treated just like the healthy subjects of Phase I and II drug trials.

Obviously this does not exhaust the ethical obligations of researchers. The PVS person is still entitled to a certain level of care and respect congruent with their status as a living human patient, and their families and friends must also be treated with compassion and care. At the very least care must be taken to ensure that normal standards of clinical practice are maintained, and that the subject is treated at all times with dignity. Families should be given a right to override or cancel prior consent if the experience becomes too distressing for them.

There is a way to conduct experiments on PVS subjects without their needing to be dead. It would still involve convincing regulators to open new consent mechanisms and convincing the public that such trials are ethically sound, but this political battle is much less radical than the attempt to convince the public that PVS patients are actually dead.

3 DRAPER H. PVS patients and research

The argument that PVS equates to death because it marks the death of the person is not a new one, but I wonder whether An Ravelingien *et al.*² need to regard those in PVS as dead to make a case for animal to human transplantation trials taking place on people in a PVS. It is not an argument likely to convince anyone who refuses to accept that human persons are the only humans who have inherent value, dignity or a right to life, and the arguments on both sides have been well rehearsed with no sign of reconciliation. My own view is that people in a PVS are still alive, albeit with a poor quality of life. I see no objection in principle to the proposal that competent individuals can decide, in advance, to take part in research when they become incompetent. At the present time, it is generally accepted that an advanced refusal of consent should be respected. There is some controversy over whether someone can insist upon treatment in advance, but in Ravelingien *et al.*'s paper, what is being proposed is not that individuals can insist on becoming research participants, but rather that they can signal a willingness to become such a participant in the future. Indeed, this principle could be extended to competent individuals like those with early onset Alzheimer's and degenerative neurological conditions who could agree in principle to the kinds of research, broadly conceived, they would be willing to be included in if and when they become incompetent in the future. Helping others by taking part in clinical research is undoubtedly a good way to live out what could be years in a PVS or other less compromised states. It may even help those for whom such a life is a virtual certainty to find meaning for the future they are destined to live.

My endorsement of Ravelingien *et al.*'s proposal is, however, cautious and based on three assumptions. First, individuals in a PVS are still alive -they should *not* be regarded as dead. Second that PVS can be diagnosed accurately and that the procedure for diagnosing it is generally accepted and uncontroversial. Third, that PVS is a permanent state and not one from which a patient, however remote the chance, could make any recovery. If this is not the case, then the Ravelingien *et al.* solution is less compelling since someone who recovers generates all the ethical problems that would be present if non-PVS volunteers

² Ravelingien, A et al. 2004 Proceeding with clinical trials of animal to human organ transplantation: a way out of the dilemma *Journal of Medical Ethics* 30: 92-98.

were used; namely that severe restrictions on lifestyle would have to be imposed for public health reasons effectively making it impossible to withdraw consent in the normal sense of the concept.

I do, however, think that there are practical problems with the proposal, hence the caution. The most obvious of these is that few, if any, people are likely to have advance warning that they will eventually end up in a PVS. For this proposal to work, therefore, many thousands of people will have to give their agreement, in principle, to be enrolled on the study should they be unfortunate enough to enter a PVS. A general agreement to donate one's body to science or medical research will not do: people in a PVS are not dead, and the research is likely to last for many years, with all the attendant strains on the participant's family. In such circumstances, however, keeping someone in a PVS alive so that they can take part in research does not raise the usual questions about the use of public resources, since I also assume that the research would either be funded by a research body, or that the health service is willing to fund such animal to human transplantation trials in light of possible future savings for the service as a whole. Accordingly, such research does not pose any burden on the health service, or if it does, such a burden has been considered beneficial in the longer term. Either way, resource concerns can be dismissed. They may, however, re-appear once the trial is over if the research participants are still alive, particularly if they are also unwilling to specify in advance that they refuse treatment such as artificial nutrition at the conclusion of the study. Is such an unwillingness a justifiable exclusion criterion for entry into the trial?

Accepting that individuals in PVS are alive would also help to resolve some of the issues raised in relation to the role of relatives. Ravelingien *et al.* are unclear about whether relatives should be able to veto the decision of the individual in a PVS. On the one hand they give weight to the likely and particular emotional reactions of the relatives to the procedures being carried out (and presumably the decade or more of life in a PVS required for such a trial to be completed). On the other they refer to occasions when the wishes of the living are not permitted to over-ride those of the dead - such as in the disposal of property through a will. However, how people choose to live their lives is not something that relatives - even close relatives such as parents or children - can justifiably veto. How someone chooses, all things being equal, to live out their life in a PVS is a matter for them alone, just as how they lived their life prior to the PVS was. Of course, people are obliged to consider the effect on others of their life-style choices, particularly those closest to them, but even when they fail to do so, relatives cannot veto these choices, and

sometimes people make decisions that, whilst taking into account the harmful effects they might have on others, they believe to be right on balance. Entering a closed religious order, emigrating, divorcing all occur despite the losses and discomfort of those closest to us, and those we hurt or disappoint have to adjust their expectations and feelings about us accordingly. Given that there is no practical burden to the relatives - having to provide daily care to the individual in a PVS, for instance - it is difficult to see what claim they have to veto the decision to take part in the research.

4 THOMPSON J. Relatives of the living dead: response to A. Ravelingien, F. Mortier, E. Mortier and J. Braeckman, 'Proceeding with clinical trials of animal to human organ transplantation'

Death in every culture has a social meaning. It is not something that concerns only the person who dies, but also his or her family, friends and other people in his community. Most people have an idea of what counts as a good death - for the person concerned and/or for those who survive. Some people would prefer to die suddenly and painlessly, in their sleep if possible. But for many people a good death involves a process in which they gradually lose their hold on life, become reconciled to their end and say goodbye to their loved ones. From the point of view of relatives and friends, a good death is likely to be one in which they have a chance to show their feelings for the dying person and to become reconciled to his loss as his life fades away. At the end of this process there is a dead body that can be put to rest in an appropriate ceremony, and then survivors are free to begin the process of learning to live without the dead person.

Problems, ethical and social, arise when the social understanding of death and how the living should relate to the dead and dying clash with medical definitions of death or the perception of dead or dying people as a medical resource. In some cultures this clash is more serious than in others. In Japan, for example, where relatives think it is important to maintain a relationship with a dying person until all signs of life cease, brain death is not accepted as sufficient to bring the relationship to an end, and, as a result, taking organs from the brain dead is generally regarded as unacceptable.³ In western countries, most people are willing to accept that brain death constitutes the end of a person's life and thus the end of their relationship with her, but there is a certain amount of unease about the matter and in some countries the wishes of the relatives prevail even in cases where the brain dead person had consented to donation.

³ Lock, M. *Twice Dead: Organ Transplants and the Reinvention of Death*. Berkeley, Los Angeles: University of California Press, 2002: 130-148.

If those who have entered a permanent vegetative state were to be used as subjects for xenotransplantation, as suggested by Ravelingien, Mortier, Mortier and Braeckman,⁴ the tension that exists even in western societies between social ideas about how to relate to the dying and medical perceptions of death (or being 'as good as dead') would reach the breaking point. Consider what relatives will be expected to endure. For security reasons they will not be able to visit the 'dead' person; they will not be able to have any physical contact with her. On the other hand, they will have a difficult time accepting that she is really dead while still showing so many signs of life. Even if they do accept that she is dead as a person, even if not biologically dead, there will be no body to put at rest, no proper ceremony of death, no appropriate end to their relationship with her. And this situation could go on for years. This is not what most people can accept as a good death.

Suppose that the person had agreed to be the subject of xenotransplantation experiments. Suppose that she put this in her living will. Do her wishes override the discomfort, inconvenience or even anguish of her relatives? In my view, they do not. Since death and dying have a social meaning, since her death is a process that involves relationships with other people, since these relationships can be extremely important for the people concerned, she is not entitled to make the decision. There are limits to individual freedom in this case as in others. Her wishes should be taken into account, but it would not be wrong for a society to allow her choice to be overruled by the wishes and concerns of those who are closely related to her. In fact, there is a stronger argument for giving decisive weight to the wishes of relatives in this case than in cases where brain dead people are used as the source of organs for transplantation. Harvesting brain dead people for organs does not so seriously disrupt the relationship of the living with the dying or the dead.

Does the prospect of being able to save many more lives by means of xenotransplantation give us good reason to override the wishes of relatives (or, for that matter, the wishes of person herself)? It is even more obvious that the answer is 'no'. To pursue the prolongation of life at the expense of relationships that give meaning and dignity to life and to death is not morally acceptable. A society should not go down that road.

⁴ A. Ravelingien, F. Mortier, E. Mortier, J. Braeckman, 'Proceeding with clinical trials of animal to human organ transplantation: a way out of the dilemma', *Journal of Medical Ethics* 2004: 30:92-98.

Nevertheless, these concerns are not reasons for prohibiting xenotransplantation experiments. Some relatives of people in a permanent vegetative state may be willing to allow their loved ones to be used in this way, especially if they believe that the person wanted this to happen and if they are persuaded of the importance of the experiment. However, consent in this case ought to be a collective commitment. Ideally, a person who would want her body to be used for such experiments if she were to fall into a permanent vegetative state ought to seek the consent of the people with whom she has a close relationship and these people ought to be fully informed about the consequences of consenting. There could be a formal process of obtaining joint consent from relatives and spouses with appropriate counselling. Alternatively, close relatives could be asked for their consent after a person who has already consented to be subjected to the experiment has lapsed into a permanent vegetative state. However, if they are unprepared and know little or nothing about what their loved one had consented to, they may be extremely distressed by the idea or may not understand what is being asked of them. Consent would be more meaningful if the people directly affected were able to make a decision in advance and together - expressing and taking into account what they regard as a good death.

5. SPARROW R. Right of the living dead? Consent to experimental surgery in the event of cortical death

Introduction

The unknown magnitude of the risk of xenozoonosis, and the difficulties involved in obtaining ethical consent to experimental surgical techniques that offer little prospect of benefit to the patient, stand as substantial barriers to the development of safe and effective xenotransplantation.⁵ As xenotransplantation offers the prospect of making life-saving replacement organs available to the tens of thousands of people who currently die each year for want of an appropriate donor organ, there is an urgent necessity to proceed as quickly as is possible with research which might contribute towards the development of safe and effective xenotransplantation.⁶ Ravelingien *et al.* are therefore to be congratulated on their contribution to resolving the difficult question as to how such research might proceed in an ethical fashion.⁷ Their controversial suggestion is that early human xenotransplantation trials should be carried out on individuals who are in a permanent vegetative state (PVS) and who have previously granted their consent to the use of their bodies in such research in the event of their cortical death. This would make it possible for xenotransplantation researchers to trial their therapies on living human bodies

⁵ Bach FH, Fishman JA, Daniels N, et al. Uncertainty in Xenotransplantation: Individual benefit versus collective risk. *Nat Med* 1998;4:141-144; Collingen P, Purdy L. Xenografts: Are the risks so great that we should not proceed? *Microbes Infect* 2001;3:341-348; Clarke MA. This Little Piggy Went to Market: The Xenotransplantation and Xenozoonose Debate. *J Law Med Ethics* 1999; 27:137-152. For a recent argument that these difficulties are not insurmountable—without experiments involving persons in a permanent vegetative state—see Rothblatt M. *Your life or Mine: How geoethics can resolve the conflict between public and private interests in xenotransplantation*. Ashgate Dartmouth: Aldershot, 2004.

⁶ The Lancet. Xenotransplantation: Time to Leave the Laboratory. *Lancet* 1999;354:1657. This is not to deny that significant ethical issues concerning the use and treatment of sentient nonhuman animals in xenotransplantation research and practice exist and remain to be resolved. For a survey, see Daar AS. Ethics of Xenotransplantation: Animal Issues, Consent, and Likely Transformation of Transplant Ethics. *World J Surg* 1997;21:975-982.

⁷ Ravelingien A, Mortier F, Mortier E, Kerremans I, Braeckman J. Proceeding to clinical trials of animal to human organ transplantation: A way out of the dilemma. *J Med Ethics* 2004;30:92-98. Page numbers in text refer to this publication.

and closely monitor the transplant recipients for any signs of xenozoonotic infection or any other unanticipated long-term effects of receiving a xenotransplant, while avoiding the difficult ethical issues which beset any attempts to trial these therapies on living persons. While they do not discuss it, it seems that the use of the bodies of individuals who are in a PVS might also advance research into other experimental therapies which hold out the prospect of significant public benefit yet involve such a high level of risk and so little hope of benefit to the individual patient in the initial trials that it would be unethical to perform them.

Unfortunately, Ravelingien *et al.*'s philosophical defence of their proposed solution is unsatisfactory in its current formulation, as it equivocates on the key question of the status of PVS patients. Ravelingien *et al.* have a bet each way on the question of whether or not individuals who are in a permanent vegetative state are in fact dead. Their proposed solution rests on the idea that it should be up to individuals to determine themselves when they should be treated as dead. Yet the authors clearly believe (and state) that PVS patients are in fact dead. Finally, given the public good their proposal is intended to achieve, the moral importance they place on the consent of an individual to the use of their body in this research is ultimately only defensible insofar as this consent represents the wishes of a living person. It is thus only a gentle caricature of their position to suggest that according to their account consent to participation in xenotransplantation research is a "right of the living dead".

While the idea that individuals should be able to consent to experimental surgery in the event of their entering a permanent vegetative state remains defensible no matter which of the positions described above we eventually settle for, Ravelingien *et al.*'s equivocation on the question of whether these individuals are living or dead means that they avoid confronting the implications of their argument. Each of these alternative positions on the status of PVS patients has important and somewhat unpalatable further implications for the treatment of such patients and for the ethics of performing experimental surgery of little expected benefit to the patient in similar cases. The solution that Ravelingien *et al.* propose to the problem of how we should proceed with xenotransplantation research is therefore not as neat as first appears.

Dead or alive?

The idea that individuals should be able to consent to the use of their bodies in xenotransplantation research in the event of entering a permanent vegetative state is suggested by current practices surrounding organ donation in the event of whole brain death (p. 96).⁸ However, the authors' proposal is likely to meet with significantly more controversy than existing practices because the experiments that they propose should be carried out are likely to appear far more grotesque in the public imagination and because the "cadavers" on which these experiments will be performed will be living, breathing bodies.

Ravelingien *et al.* acknowledge that the extension of the notion of death from circulatory death to whole brain death was itself controversial and that any extension to treat patients in permanent vegetative states as dead is likely to be even more so. In anticipation of this controversy, they argue -following a suggestion of Veatch's- that individual and cultural differences in attitudes towards the moment of death should be respected by allowing individual patients to decide for themselves when they should be treated as dead (p. 96).⁹ If they decide that (for them) death occurs when they have suffered an irreversible loss of consciousness and regardless if they continue to have respiration and a pulse even in the absence of mechanical assistance, then they should be able to donate their body to xenotransplantation research just as individuals may currently donate their body to science in the event of their (circulatory or "whole brain") death. The advantage of this proposal is that it seemingly avoids the necessity of resolving the difficult philosophical and political debate about the status of these patients. It also explains the importance the authors place on gaining the consent of the PVS sufferer for participation in experimental xenotransplantation.

⁸ Fost also discusses the possibility that we might proceed with sourcing organs from persons in a PVS, if they had previously consented to such. Fost N. Reconsidering the Dead Donor Rule: Is it Important That Organ Donors Be Dead? *Kennedy Inst Ethics J* 2004;14:249-260, at 253-4.

⁹ Veatch RM. The conscience clause: how much individual choice in defining death can our society tolerate? In: Youngner SJ, Arnold RM, Shapiro R, eds. *The definition of death: contemporary controversies*. Baltimore: John Hopkins University Press, 1999:140, cited in Ravelingien A, Mortier F, Mortier E, Kerremans I, Braeckman J. Proceeding to clinical trials of animal to human organ transplantation: A way out of the dilemma. *J Med Ethics* 2004;30:92-98 at note 61.

The obvious difficulty with this move is that it is *prima facie* implausible that whether or not someone is dead is a matter of individual choice. While death is a more complex phenomenon than first appears, especially in the light of advances in medical technology, it remains fundamentally a category of natural science rather than of ethics.¹⁰ As such, it is an objective rather than a subjective matter. To the extent that the definition of death does involve making value judgements, these are primarily social rather than individual questions.¹¹ That is, they are questions about how other people should treat and respond to a person in a particular condition. When is it appropriate to bury someone, or to mourn them, or to extract their organs for transplant? These are questions that societies or cultural groups, rather than individuals, have to answer. Indeed, insofar as they necessarily involve the disposition and behaviour of large numbers of strangers, they are questions that individuals *cannot* answer.

Although it may not be possible for individuals to settle the question of when they are dead, it *is* possible to grant them some power to determine when they should be treated as though they are dead and what can be done to them when they are. This is presumably what Ravelingien *et al.* intend, rather than the stronger and less plausible thesis that individuals should be allowed to determine when they *are* dead. Yet, even here, there are important limits on individuals' rights to determine when they should be treated as dead. We don't allow people to decide that their bodies should be available to train medical students in dissection while they are still conscious, for instance. Similarly, in societies that do use a "whole brain" criteria of death, while the medical profession may respect the wishes of deceased individuals, not to procure organs from them if they should suffer whole brain death, they do not typically allow them to insist on continuing ventilation and medical support on the ground that they are still alive at this point. The question remains

¹⁰ Singer P. *Rethinking Life and Death*. Melbourne: The Text Publishing Company, 1997:20-22. . This is not to deny for a moment the extent of the controversy surrounding the definition of death, or the possibility that there is more than one reasonable position on the matter. However, it is to insist that what the controversy is about is a distinction which plays a fundamental role in the life sciences and which requires a definite resolution (Russell T. *Brain Death: Philosophical Concepts and Problems*. Aldershot, UK: Ashgate Publishing Ltd, 2000, cited in Campbell CS. *A No-Brainer: Criticisms of Brain-Based Standards of Death*. *J Med Philos* 2001;26:539-551 at 548).

¹¹ Campbell CS. *Harvesting the Living?: Separating "Brain Death and Organ Transplantation*. *Kennedy Inst Ethics J* 2004;14:301-318, at 314; Lock, M, and C Honde. *Reaching Consensus About Death: Heart Transplants and Cultural Identity in Japan*. In: Weisz G ed. *Social Science Perspectives on Medical Ethics*. Dordrecht: Kluwer Academic Publishers, 1990:99-119, at 100; Machado N. *Using the bodies of the dead: legal, ethical, and organisational dimensions of organ transplantation*. Aldershot, Hampshire, England: Ashgate/Dartmouth, 1998:4

then, why cortical death should be held to be within the realm where it is appropriate to allow individuals to decide whether they should be treated as dead or not.

The authors suggest, again following Veatch, that an individual's right to determine when they should be treated as dead should be confined to reasonable claims, with the clear presumption that it is reasonable to treat PVS sufferers as either dead or alive (p. 96). However, it is unclear what this restriction on claims about death would amount to, given the range of different opinions on when people are dead. Some religious worldviews believe that dying is a process which does not reach its end until a point long after that at which an individual has stopped breathing.¹² Other people, perhaps including a significant proportion the medical community, believe that it is clearly the case that people are dead when they have no higher cortical functions.¹³ In an age when human cloning via somatic cell nuclear transfer is close to becoming a reality, cellular death may mark an important point prior to which there is some hope of resurrection of at least part of what people care about when they think about their mortality. In the face of such wide-ranging disagreement, it is difficult to settle the bounds of the "reasonable". Indeed, there is almost as large a range of opinion about what the bounds of the reasonable are in relation to beliefs about death as there is about the moment of death itself. Given that death is primarily a matter of natural science and, to a lesser extent, a social consensus, any attempt to settle disagreement about the limits of reasonable beliefs about death must inevitably refer to the matters of fact which underpin claims about death and the social practices which constitute our response to it.¹⁴ Pointing to disagreement about the status of PVS patients therefore only partially mitigates the necessity of settling the question of whether or not they are dead before we can decide whether it is reasonable to treat them as such.

¹² Lock, M, and C Honde. Reaching Consensus About Death: Heart Transplants and Cultural Identity in Japan. In: Weisz G ed. Social Science Perspectives on Medical Ethics. Dordrecht: Kluwer Academic Publishers, 1990:99-119, at 110.

¹³ Singer P. Rethinking Life and Death. Melbourne: The Text Publishing Company, 1997:32-35; Youngner SJ, Landfield CS, Coulton CJ, et al. "Brain Death" and Organ Retrieval. A Cross-Sectional Survey of Knowledge and Concepts among Health Professionals. JAMA;261:2205-2210, cited in Fost N. Reconsidering the Dead Donor Rule: Is it Important That Organ Donors Be Dead? Kennedy Inst Ethics J 2004;14:249-260 at 250; Siminoff LA, Burant C, Youngner SJ. Death and Organ Procurement: Public Beliefs and Attitudes. Kennedy Inst Ethics J 2004;14:217-234.

¹⁴ Campbell CS. Harvesting the Living?: Separating "Brain Death and Organ Transplantation. Kennedy Inst Ethics J 2004;14:301-318, at 314.

However, the real problem with settling questions about the status of PVS patients by allowing people to decide for themselves when they should be treated as dead is that whatever they decide, they are in fact either dead or alive. Importantly, how we should respond to their desire as to how they should be treated depends to some extent on whether they are dead or alive. The wishes of the living and the dead have significantly different moral weights.¹⁵ Ravelingien *et al.* therefore cannot avoid resolving this question.

Dead?

In fact, Ravelingien *et al.* do make it clear at a number of points in the paper that they believe that a person who is in a permanent vegetative state is in fact dead. To be precise, they believe that cases of PVS present us with a situation in which a person has died leaving behind a living human body. Individuals in a permanent vegetative state have lost all those properties and/or capacities (sentience, rationality, and the ability to relate to others) that may plausibly be thought to be constitutive of personhood and to justify the moral respect that persons are owed. Moreover, because persons in a permanent vegetative state lack sentience, they no longer possess interests. Consequently, they cannot be harmed in the course of xenotransplantation research (p. 95). It is merely a strange matter of circumstance that their bodies retain properties such as respiration, circulation, and other autonomic nervous reflexes, that are normally associated with people who are alive. Given that people who have entered permanent vegetative states are dead it is reasonably straightforward to conclude that individuals should be able to will their remains to xenotransplantation research in the event of their cortical death just as they may to other forms of medical research in the event of their whole brain or circulatory death (p. 95).

Amongst a philosophical readership, this conclusion will hardly appear surprising. The authors themselves note that the argument that PVS patients are in fact dead and that

¹⁵ Machado N. Using the bodies of the dead: legal, ethical, and organisational dimensions of organ transplantation. Aldershot, Hampshire, England: Ashgate/Dartmouth, 1998:176. Harris J. Clones, Genes and Immortality: Ethics and the Genetic Revolution. Oxford: Oxford University Press, 1998:123.

consequently their organs should be available to be sourced for transplantation has been made a number of times before (p. 95).¹⁶ But what is now thrown into question is why the authors have restricted the range of cadavers available for xenotransplantation research to those where the recently deceased had provided their explicit consent to their remains being used in such research. Why is it so important that an individual's consent has been obtained? At the very least it seems that, in nations which operate an "opt out" rather than an "opt in" system of organ collection after death¹⁷, a strong argument could be made that the bodies of individuals who are in a PVS should be made available for xenotransplantation research unless they have explicitly directed otherwise. If the benefit to the public of increasing the number of organs available for transplantation justifies a change in the presumption of consent for organ donation then the same is likely to be the case for participation in xenotransplantation research.

The moral weight of the wishes of the dead

In fact, the implication of declaring PVS patients to be dead is more radical than this. Where people do not wish their cadavers to be used for xenotransplantation research, our reason for respecting this desire involves respect for the wishes of the dead. While there *are* reasons for respecting the wishes of the dead, these have always been somewhat philosophically controversial, given that the dead will experience no harm if their wishes are not respected (pp. 95-97).¹⁸ This in turn suggests, especially to those with leanings

¹⁶ See, for instance, Council on Ethical and Judicial Affairs AMA. The use of anencephalic neonates as organ donors. *JAMA* 1995;273(20):1614-1618; Fost N. Reconsidering the Dead Donor Rule: Is it Important That Organ Donors Be Dead? *Kennedy Inst Ethics J* 2004;14:249-260; Hoffenburg R, Lock M, Tilney N, et al. Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997;350:1320-1321; Singer P. *Rethinking Life and Death*. Melbourne: The Text Publishing Company, 1997:38-50; Rothblatt M. *Your life or Mine: How geoethics can resolve the conflict between public and private interests in xenotransplantation*. Ashgate Dartmouth: Aldershot, 2004:11.

¹⁷ Machado N. *Using the bodies of the dead: legal, ethical, and organisational dimensions of organ transplantation*. Aldershot, Hampshire, England: Ashgate/Dartmouth, 1998:44-47 provides an account of the how different nations in Europe, Australia and North America determine the standard of consent required for organ donation.

¹⁸ See, for instance, Levenbook BB. Harming Someone after His Death. *Ethics* 1984;94(3):407-419; Partridge E. Posthumous Interests and Posthumous Respect. *Ethics* 1981;91(2):243-264.

towards utilitarianism, that the interests of the dead should be discounted somewhat when they come into conflict with the interests of the living.¹⁹

As Ravelingien *et al.* have emphasised, the living may have very substantial interests in large numbers of xenotransplantation trials being performed as quickly as is practicable. It is puzzling then why the authors are so quick to concede that the wishes of the deceased should be allowed to stand in the way of this.

Note that the balance of considerations in relation to the use of PVS cadavers²⁰ in xenotransplantation research, against the wishes of the deceased individual, is significantly different than those when it is organ collection from patients who have suffered whole brain death which is at issue. Collection of organs from a cadaver may save a few lives at most. Given the revolutionary life-saving potential of xenotransplantation, research on PVS cadavers might save tens of thousands of lives. Indeed, it is precisely because Ravelingien *et al.* believe this to be the case, that they have put forward their proposal. Of course, drafting any individual PVS cadaver into this research may not save all these lives, but it *might* well be the case that it will make a more important contribution to the reduction of human suffering than would the use of this cadaver's organs alone. The reasons in favour of co-opting the remains of those who have died by entering a PVS—regardless of their consent—are therefore much stronger than those justifying the sourcing of organs for transplant without consent.

It is true that many societies do give a substantial moral weight to the wishes of the deceased in relation to the treatment and disposal of their remains. The public's ideas about what is mandated by the notion of respect for the dead are often much stronger than the justifications usually provided for them by philosophers allow. Despite this, decisions about the treatment of the body of the deceased against the deceased's wishes are far from unprecedented. It is already firmly established that significant and pressing public health interests may override individuals' wishes about the disposal of their

¹⁹ Harris J. Clones, Genes and Immortality: Ethics and the Genetic Revolution. Oxford: Oxford University Press, 1998:123.

²⁰ It is difficult to know how to refer to the bodies of individuals who are in PVS, as their status is the central issue in the controversy under discussion. However, in this section, where I am discussing the possibility that such individuals are dead, "cadavers" does not seem inappropriate.

remains. Thus, for instance, when the cause of death of a particular individual is unknown but where the involvement of a dangerous infectious agent is suspected, or where a death has occurred as the result of a criminal act, coroners may be required to perform an autopsy regardless of the wishes of the deceased.²¹ On the other hand, as Ravelingien *et al.* point out, some countries, such as New Zealand, allow that the relatives of the deceased can override the wishes of the deceased to donate their organs for transplant or research.

Our willingness to override the wishes of the deceased in other circumstances suggests that Ravelingien *et al.*'s concern for the consent of the deceased individual for the use of their remains is exaggerated here. Their belief that PVS sufferers are in fact dead, alongside their recognition of the large public benefit that would be achieved by proceeding quickly to human xenotransplantation trials, should push them towards the much more radical claim that PVS cadavers should be made available for xenotransplantation research *regardless* of the wishes of the deceased.²²

Respect for the wishes of the relatives?

One obvious and important objection at this point, of course, is that while the wishes of the deceased may be overridden by the benefits to the public of proceeding with xenotransplantation trials, there is also the matter of the wishes of their living relations. The partner, parents or siblings of the deceased may be understandably distraught at witnessing the still-beating heart or working lungs of their recently dead relative being removed from their body and replaced with the organs of genetically modified pigs.

However, again, there is a familiar range of cases where we neglect the wishes of relatives concerning the treatment of the remains of the deceased. Ravelingien *et al.* themselves

²¹ In Victoria, Australia, the circumstances in which autopsies are permitted and/or required are set out in the Coroners Act 1985. A discussion of the legal status of bodies and the circumstances in which the consent of the individual can be overridden in the service of the public interest in the Swedish context is provided in Machado N. Using the bodies of the dead: legal, ethical, and organisational dimensions of organ transplantation. Aldershot, Hampshire, England: Ashgate/Dartmouth, 1998:171-183.

²² Harris J. Clones, Genes and Immortality: Ethics and the Genetic Revolution. Oxford: Oxford University Press, 1998:125.

note with approval that many countries allow the wishes of the deceased concerning the disposal of their remains priority over the wishes of their living relatives (p. 97) (contra the example of New Zealand, which they cite to a different purpose). The interests of other parties may also justify denying the wishes of relatives. We do not allow relatives to discard the body of the deceased in the street or to make ornaments out of it, no matter how strongly they desire to. Remains may be buried or cremated without consulting relatives if failing to do so will constitute a threat to public health or safety. Where public health, or the investigation of a possible homicide, requires it autopsies may be performed against the wishes of relatives.

The wishes of living relatives are an important concern when we attempt to assess the balance of considerations surrounding the treatment of the remains of the deceased, but they are not the only consideration. Where the public interest is large enough, we may sacrifice the interests of the relatives for the greater good of the community.²³ The harm to the living relatives may be minimised by ensuring that they are aware of the justification for the treatment of the deceased and the good it accomplishes, in the hope that this will cause them to reconsider their opposition to actions taken to this purpose.

Public policy reasons for respect for the dead?

A significant concern about policies regarding the use of cadavers is the impact that they may have on the willingness of individuals to donate their remains to science or, more importantly, to enter into a medical and/or hospital environment at all. If people suspect that their wishes concerning the disposal of their remains will not be respected after they die they may be reluctant to remain in hospital if they are dying.

However, the relative frequency of the PVS condition compared to circulatory or whole brain death will have a significant impact on consequentialist calculations about the effects that compulsory requisition of cadavers will have on the living. Policies concerning the treatment of the cortically dead are likely to affect far fewer people than policies regarding those who have suffered circulatory or whole brain death. The vast majority of

²³ Harris J. Clones, Genes and Immortality: Ethics and the Genetic Revolution. Oxford: Oxford University Press, 1998:125.

people will not end up in a permanent vegetative state and, to the extent that they recognise this, may judge that what might happen to them if they do enter into such a state is not of sufficient concern to prevent them from seeking medical care when they need it.²⁴ While the impact of proceeding with xenotransplantation research involving PVS cadavers without the consent of the deceased on the willingness of individuals to enter a medical setting would need to be monitored, there is little reason to believe that this will be so significant as to outweigh the public benefits to be gained by carrying out xenotransplantation trials.

Another, I think more pressing, concern is that if xenotransplantation was to become associated in the public mind with such macabre practices as transplanting animal organs into the living bodies of the recently deceased against the wishes of the deceased, this might have disastrous impact on public support and therefore funding for xenotransplantation research. Proceeding with xenotransplantation trials involving PVS cadavers without the consent of the deceased (and perhaps also their relatives) would then be self-defeating, as it would undercut support for the very research it was aiming to advance.

However, this reason to respect the wishes of the dead concerning the disposal of their remains depends crucially both on some empirical facts about the link between experimentation on PVS cadavers and public support for xenotransplantation and on resisting alternative courses of action that might sever this link. It may simply not be the case that public support for xenotransplantation will collapse if the research necessary to prove its safety involves experimenting on deceased individuals in permanent vegetative states against their previously declared wishes. The prospect of resolving the problem of the scarcity of donor organs available for transplantation that xenotransplantation holds out may be sufficiently attractive to the public that they would continue to support xenotransplantation research involving PVS cadavers even if this takes place against the wishes of those whose remains are being used for this purpose.

More problematically, it may be possible for xenotransplantation research involving PVS cadavers to proceed without any impact on popular support for xenotransplantation if the

²⁴ They may also rightly reason that if such experiments are performed on them they will remain unaware of it and, arguably, unharmed by it.

public remains unaware of it. If the expected public benefit from xenotransplantation research is large enough, it seems as though researchers may have reason to ignore even the explicit instructions of relatives and proceed with xenotransplantation research involving PVS cadavers *without* their consent and without their knowledge. That is, they may be justified in proceeding with *clandestine* xenotransplantation research. This might involve, for instance, telling the relatives that their relation had died (and providing them with a body for burial) and then abducting the PVS cadaver for research at a secure location.

The argument here is analogous to an argument that might have been made in favour of the theft of corpses for early medical research and dissection in the 17th, 18th and 19th centuries. The methods used to procure cadavers for dissection, which included theft, deception and perhaps—in some cases—murder, were *prima facie* immoral.²⁵ However, it might well be argued that the apparently immoral actions of these researchers and their body snatching accomplices were ultimately justified by the immense public benefit that has been secured by modern medicine on the basis of knowledge gained from their activities. Dedicated xenotransplantation researchers might reason that they are in a similar position today. While it is normally wrong to deceive people about the fate of their (or their relations) remains, the benefits of proving xenotransplantation safe are so great that if the only way to carry out the necessary trials without xenotransplantation research falling victim to a public backlash which would prevent it from reaching its goals is to do so clandestinely, then such deception may well be justified. The consequentialist tone of Ravelingien *et al.*'s paper suggests that they may have difficulty resisting this conclusion.²⁶

Of course, there may be many other good ethical reasons not to pursue this policy. I am not seriously proposing it as a way forward for xenotransplantation research. My purpose in raising the possibility has solely been to show that there is a significant tension between Ravelingien *et al.*'s claims that individuals who are in a permanent vegetative state are dead and that there is an enormous public benefit to be gained by performing

²⁵ MacDonald H Human Remains: Episodes in human dissection Melbourne: Melbourne University Press, 2005.

²⁶ Indeed, recent scandals in the UK suggest that at least some in the medical and research communities have embraced it. MacDonald H Human Remains: Episodes in human dissection Melbourne: Melbourne University Press, 2005:186-89.

xenotransplantation research on the “living dead”, and their claim that it is essential to secure the prior consent of the deceased for participation in such research.

Alive?

One way to justify the authors’ concern for the consent of PVS patients is to concede that these individuals are still alive. By virtue of the fact that their heart beats and their lungs respire unaided, they are still “one of us”, a living human being and as such a member of a community whose respect for each other in a medical context is expressed in a concern for consent to treatment. In some ways this is not a terribly attractive philosophical position to hold given that, as we observed above, persons who are in a permanent vegetative state seem to have so few of the morally significant properties that ground respect for living human beings. In defence of this position, however, it should be noted that PVS sufferers remain legal persons.²⁷ We also have strong intuitions that despite their lack of sentience they are—in some sense at least—alive and that for this reason to experiment upon them while they are in this state without their consent is more morally problematic than if they were dead.

If PVS patients are in fact alive this need not lead to the conclusion that they may not volunteer their bodies for xenotransplantation trials. It might be argued, for instance, that while they are alive and that their previously expressed wishes are worthy of respect because of this, they are also in the unique position of having very few, if any interests, once they are in a permanent vegetative state. They will not suffer any harm even if participation in xenotransplantation research leads to their death. Thus as long as they consent to such research taking place there are no reasons of a paternalistic nature to object to their participation in it.²⁸

²⁷ Singer P. *Rethinking Life and Death*. Melbourne: The Text Publishing Company, 1997:27; Hoffenburt R, Lock M, Tilney N, et al. Should organs from patients in permanent vegetative state be used for transplantation? *Lancet* 1997;350:1320-1321.

²⁸ I owe this point to Neil Levy who made it in a seminar at the Centre for Applied Philosophy and Public Ethics, at the University of Melbourne, at which An Ravelingien presented her and her co-authors’ ideas.

However, any argument that it is legitimate for PVS sufferers to consent to participation in xenotransplantation research is likely to lead to further, stronger conclusions about the rights of individuals to volunteer for experimental surgery when doing so is unlikely to harm their interests. There are, after all, other circumstances in which - it might be argued - that people are unlikely to be harmed by participation in experimental research even when it offers them little hope of benefit. Most obviously, if individuals are dying of organ failure, with no prospect of sourcing a human organ for transplant surgery, then receiving a xenotransplant is unlikely to make them worse off. Despite this, they may be willing to consent to participate in research for altruistic reasons in the hope that their participation will assist in the development of a technology which will provide benefits to others in the future. If what justifies experimentation on persons in a permanent vegetative state is that they are unlikely to suffer any harm in the process then consent to altruistic participation in experimental medical research in cases of medical extremity will also be permissible.²⁹

This conclusion in itself is not especially surprising. There is an ongoing debate about the morality of allowing patients to participate in research which is unlikely to provide them with any benefit if their motives are altruistic. However, altruistic participation in research in a situation of medical extremity is also generally recognised to be ethically fraught and to open individuals to the danger of exploitation. Further argument is therefore required before we can accept this possible implication of the authors' argument. More importantly, for the purposes of this discussion, the conclusion that it is ethical to allow individuals to volunteer for participation in research in a situation of medical extremity will remove much of the need for xenotransplantation trials to involve individuals who are in a permanent vegetative state in the first place, as research into the dangers of xenozoonosis and other long-term health effects on transplant recipients could now be performed on living patients with their consent.

²⁹ The argument here presumes that harm that is measured according to a baseline of interests which would exist independently of the action being considered.

Conclusion

None of this discussion is intended as a direct criticism of Ravelingien *et al.*'s proposal as to how xenotransplantation research might proceed past the current ethical impasse. From a public policy perspective, it seems likely that the proposal that we attempt to secure the consent of individuals to allow their remains to be used for research purposes should they enter into a permanent vegetative state is indeed the best way of ensuring public support for xenotransplantation research involving human bodies in a permanent vegetative state. However, the argumentative route that they take to this conclusion is confused. The existence of controversy concerning the status of individuals who are in a permanent vegetative state is itself insufficient to justify the conclusion that it is legitimate to trial experimental surgery on them as long as their consent is secured. The underlying philosophical question remains the status of these individuals. If we decide that they are in fact dead then it seems that the requirement for their consent is weaker than Ravelingien *et al.* indicate and that, given the large public benefit to be gained from developing xenotransplantation technology, we may need to look further at the possibility that research would be justified *without* the consent of the deceased. If we decide that they are in fact alive then the authors' concern that we seek their consent is better founded. However, allowing that such research is ethical suggests that it may also be ethical to proceed with experimental surgery involving consenting individuals in other circumstances of medical extremity and consequently that the need for xenotransplantation trials to be conducted on individuals who are in permanent vegetative states is less pressing than the authors suggest. Significant philosophical work therefore remains to be done before we can properly assess the ethics of proceeding to human trials of xenotransplantation involving individuals in a permanent vegetative state. By drawing attention to the issues, Ravelingien *et al.* have made an important contribution to this project.