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THE ETHICS AND REGULATION OF HUMAN EMBRYONIC STEM CELL RESEARCH: A CRITICAL ANALYSIS OF THE DEBATE

by
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DISSERTATION SUBMITTED IN FULFILMENT OF THE DEGREE
OF DOCTOR OF PHILOSOPHY AT GHENT UNIVERSITY

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TO MY PARENTS

ACKNOWLEDGMENTS

Writing this dissertation has been an exciting, but sometimes lonely journey that I could not have undertaken without the enduring support of my colleagues, friends and family.

I wish to thank my supervisor, Prof. Dr. Freddy Mortier, for encouraging me to pursue a topic of personal interest, and for giving me a free hand in my research. I have greatly appreciated his confidence in me, and his lucid and illuminating suggestions. Despite his obligations as the Dean of our Faculty, he always made time for me, to answer my questions and give me advice, for which I am ever grateful.

I wish to express my warmest appreciation to Prof. Dr. John Harris (University of Manchester), who has never ceased to support me since we first met at the Third International Conference of Bioethics in Taiwan in 2002. His in-depth guidance, never-ending enthusiasm and incredible sense of humour helped me through the difficult times. I have greatly benefited from his writings, and I am very grateful for his constructive criticism and helpful advice.

I am greatly indebted to Prof. Dr. Julian Savulescu (University of Oxford), who gave me the opportunity to spend two months at the Oxford Uehiro Centre for Practical Ethics. Working in such a stimulating and challenging intellectual environment proved to be an invaluable experience. Prof. Savulescu's unwavering interest, thought-provoking questions and inspiring advice were a great help.

I am also obliged to Dr. Neil Levy and the rest of the team of The Centre for Applied Philosophy and Public Ethics (CAPPE) in Melbourne for giving me the opportunity to stay at the centre and exchange ideas.

I wish to acknowledge and thank Prof. Dr. Johan Braeckman (Ghent University). Five years ago, he offered me the opportunity to be the co-author of a book on the ethics of human cloning. This proved to be a timely writing experience that bolstered my confidence and encouraged me to proceed with my research in bioethics.

I also wish to express my gratitude to Prof. Dr. Jonathan Glover (Kings College, London) for his support and encouraging words. I will always keep them in mind.

Furthermore, I wish to thank Dr. Peter Ponsaerts (University of Antwerp) and Dr. Chris Ward (The University of Manchester), who guided me through the complexities of stem cell science and read parts of my work to verify the scientific claims. I have profited from a very challenging interchange of scientific and philosophical ideas with Chris during the process of writing our paper.

During the preparation of this work, several people have invited me to give seminars and public lectures, from which I have greatly benefited through challenging discussion.

I cannot thank them all here, but I would like to express my gratitude to Prof. Dr. Shui Chuen Lee for inviting me twice to the International Conference on Bioethics in Taiwan, which opened up plenty of opportunities for my research.

In addition, I have benefited from the helpful suggestions, comments and support of the following people: Dr. Lisa Bortolotti, Dr. Nick Bostrom, Isa Cossement, Dr. Nikolay Dentchev, Dr. Charles A. Erin, Dr. Susan Hawes, Prof. Dr. Søren Holm, Prof. Dr. Ludger Honnefelder, Dr. Inigo de Miguel, Prof. Dr. Guido Pennings, Prof. Dr. Peter Singer, Dr. Margaret Sleeboom, Prof. Dr. Sigrid Sterckx, Dr. Tuija Takala, Dr. Giuseppe Testa, and Prof. Dr. Bob Williamson.

Furthermore, I wish to thank my fellow PhD students and friends from Ghent University for their support: Kristof Van Assche, Farah Focquaert, Debbie Mannaerts and An Ravelingien.

Special thanks are due to Filip Coopman, who developed the lay-out for this dissertation and for a poster that won me the first prize on the first doctorandi colloquium.

Apart from the above-mentioned people, I could never have finished this dissertation without the continuous support of my friends and family. Writing a PhD thesis and the activities surrounding it can be stressful, not just for the candidate, but also for the people around her. I wish to thank the 'Jan Palfijn team' for moral support every time I took up a new challenge: Karine, Claire, Gerda and all the others whom my mother convinced of the importance of keeping their fingers crossed for me. I also wish to express my appreciation to the 'Waterkant team': Cin & An. Their support and the time they gave over to listening to me were a great encouragement. I wish to thank Liza, who recently became a doctor of philosophy, and who, having first-hand knowledge of what I was going through, was able to give me good, empathetic advice.

Writing a PhD dissertation is a demanding task, not only academically but also personally, and emotions can become intense, especially during the last months of writing. I wish to thank Lot, Sven, Kris, Zus and Grant for their support and for diverting me in stressful times. Their friendship gave me the strength to get through the most trying periods.

I dedicate this dissertation to my parents, for their love.

Katrien Devolder
Ghent, November 14, 2005

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LIST OF ABBREVIATIONS

ANT: altered nuclear transfer
ART: assisted reproduction techniques
AS cell: adult stem cell
DBA: diamond blackfan anaemia
DCD: discarded-created distinction
DNA: deoxyribonucleic acid
EG cell: embryonic germ cell
ES cell: embryonic stem cell
hES cell: human embryonic stem cell
HFEA: Human Fertilisation and Embryology Authority
HLA: human leukocyte antigen
HSC: haematopoietic stem cell
ICM: inner cell mass
IVF: in vitro fertilisation
MAPCs: multipotent adult progenitor cells
MHC: major histocompatibility complex
NBAC: National Bioethics Advisory Commission
NIH: National Institutes of Health
PCBE: President's Council on Bioethics
PGD: preimplantation genetic diagnosis
SCNT: somatic cell nuclear transfer
UCB: umbilical cord blood

INTRODUCTION

1. ISSUES AT STAKE

This dissertation is about the 'stem cell debate' that is, the debate over the ethics of the generation and use of all types of stem cells, in particular *human* stem cells. The stem cell debate has an unprecedented importance. Three reasons underlie this claim.

1.1. The Holy Grail of medicine

First, stem cell research will have an enormous impact on almost all aspects of medicine. Stem cells are unspecialised ('blank') cells that can self-renew in their natural state, but which can also generate specialised cell types of the body, such as heart cells or liver cells. They can be found in humans from the moment of conception until after death. Because of their unique capacities they open up radically new avenues for studying human disease, for developing treatments for currently incurable diseases and conditions, and for drug testing. The probable role for stem cells consists not principally in merely halting disease, rather, stem cells could be used to repair or replace damaged tissues and organs. One day it may even be possible for our body to restore itself, in the way that zebra-fish and salamanders can re-grow entire limbs and organs. No wonder that stem cell research has been described by many as the Holy Grail of medicine. Most promises of stem cell research, however, are still far from being realised, and it is not even certain whether or not they ever will be. Although worldwide, a great many scientists are committed to stem cell research and discoveries and progress continue to be made, stem cell research is still largely in the experimental stages. Chapter I provides a summary of the science and the current state of the art of stem cell research. A good understanding of the science is often missing from the debate process. However, it should be noted that the research is moving at such a fast pace that it is barely possible to keep up with the science, which is also becoming increasingly complex. This is problematic, as a thorough understanding of the 'facts' is essential for the establishment of an accurate viewpoint on the ethics. Moreover, many of the facts about stem cells are not presently known. As we will see throughout this dissertation, this genuine scientific uncertainty is a crucial factor in the stem cell debate. Decisions about which line of research should proceed or be given priority have to be taken in the face of this scientific uncertainty. On the other hand, these uncertainties will not be resolved if certain types of research cannot be done because of prohibitive or restrictive regulations. This is the catch-22 for scientists who want to prove the promising potential of controversial types of stem cell research.

What exactly are the controversies raised by stem cell research? Stem cell research creates ethical and policy concerns associated with every advance in biomedical research, including concerns relating to the ethical conduct of basic and clinical research, justice and resource allocation, equal access to healthcare, intellectual and other property rights, and public accountability. Although of great importance, these issues have not been central in the stem cell debate so far.

The controversy raging in the stem cell debate is not around the issue of *whether* stem cells should be used for protecting and improving people's health, but around *which source* of stem cells can be used

to achieve this goal. The use of stem cells from humans after birth (adult stem cells) has so far remained uncontroversial. (This may change, however, if they radically prolong life). Adult stem cell research falls under the heading of research with human subjects, for which adequate regulation and protection exists in most countries. As in bone marrow transplantation and organ donation - both widely accepted practices - the main issues are those of free and informed consent and of privacy and confidentiality of personal data. The use of fetal stem cells does not raise any new ethical issues of substance either and, in most countries, is covered by existing regulations on fetal tissue research. As in fetal tissue research, the main issue is the link with the preceding abortion. To guarantee the separation between the abortion and the subsequent use of the fetal tissue, most countries have implemented safeguards to reduce the risk that the woman's decision to abort is unduly influenced by the possibility to donate the fetal tissue. This has led to a relatively broad acceptance of the use of aborted fetuses to obtain fetal tissue and, subsequently, fetal stem cells.[1]

So far, only stem cells from one particular source have set off a storm of controversy, hence they became the primary focus of the stem cell debate, and of this dissertation.

In 1998, a team of researchers at the University of Wisconsin led by James Thomson was the first to establish human embryonic stem (hES) cells.[2] As the name suggests, these cells are derived from human embryos. This breakthrough combined with the announcement of the birth of Dolly the cloned sheep one year before,[3] which proved that mature body cells could be turned back to an embryonic state, enabled scientists fully to realise the enormous potential of hES cells for medicine. Because of their unique capacity to give rise to virtually any cell type in the body (their pluripotency), and their ability to expand indefinitely in the laboratory without losing their pluripotency (their immortality), hES cells could offer a potentially unlimited source of body cells for use in transplantation therapies as well as providing a useful model system for elucidating mechanisms involved in human development and disease. Moreover, by combining hES cell technology with cloning, scientists could generate replacement cells and tissues that are genetically identical to those of the patient and which consequently, will not be rejected after transplantation. This would help to overcome two major hurdles in organ transplantation: the acute shortage of donor organs and the huge risks and inconveniences associated with immunorejection. Is it any wonder that Thomson's achievement has caused great excitement worldwide?

However, not everyone reacted with equal enthusiasm. At the same time, thomson's hes cell breakthrough set off a storm of protest worldwide. The reason is that, to date, hes cells can only be derived from human embryos through a process that necessarily destroys the embryo. For many people this need not be an insurmountable problem, as they believe that embryos, under certain conditions, can be used for beneficial purposes. For some people, however, it constitutes the main reason to radically oppose hS cell research. In their view, embryos should never be used as a mere means to the ends of others, however valuable these may be. Worldwide, they are lobbying for the legal prohibition of hES cell research.

One suggested solution to the problem of 'killing' embryos in stem cell research is simply to opt for less controversial ways of obtaining stem cells. This solution, however, is too quick as there is still scientific uncertainty over which line of research is most promising. Until now, no stem cells from alternative sources have been identified that possess the same functional capacities as hES cells and that can meet the need for research with hES cells to reach the intended research goals.

This results in the principal ethical dilemma in hES cell research: on the one hand there is growing consensus that hES cells hold unique promise for some therapies and certain types of research that other types of stem cells cannot provide; on the other hand there is the controversial issue of 'killing' human embryos in order to obtain hES cells. To find a way out of this dilemma one cannot avoid the question: what constitutes the value of an embryo and why cannot we use it as a means to derive stem cells? The embryo debate has once again become very topical.

This brings us to the second reason why the stem cell debate is of great significance.

1.2. Re-ignition of the 'embryo-debate'

The stem cell debate combines many of the most contentious bioethical issues ever discussed, most pivotal of which is the issue of the moral status of the embryo, which has been the subject of heated debates in the context of contraception, abortion, fetal tissue research and assisted reproduction for more than thirty years. The fact that these older discussions have been reignited has been a crucial factor in the stem cell debate. The reason is that every justification for an ethical stance on hES cell research will inevitably touch on earlier justifications of moral positions and public policies on related practices where the protection or the vulnerability of the embryo is at stake. This in itself need not be problematic as one would expect countries with very liberal policies on abortion and assisted reproduction techniques (ART) to adopt an equally liberal policy on the basis of similar justifications with regard to hES cell research and the same could be expected from countries that already have restrictive policies on embryo protection. The course of the stem cell debate, however, has shown this is not necessarily the case. For countries with restrictive regulations with regard to embryo protection in the context of abortion and ART have not necessarily been the most restrictive with regard to hES cell research. The difficulty then lies in the justification of allowing some hES cell research without violating the spirit of the existing laws or regulations. If the latter rely on the view that human embryos have special moral status, destroying embryos in the context of hES cell research needs strong justification. The underlying problem is that once one allows the generation and use of embryos for particular beneficial purposes, it becomes very hard to justify a ban on generating and using embryos for morally equivalent purposes. This difficulty is also encountered in countries that allow abortion and ART but seek to justify severe restrictions with regard to hES cell research.

1.3. We may all benefit

The third reason why the stem cell debate is of unprecedented importance is that stem cell research,

compared to other areas of biomedical debate, including abortion and assisted reproduction, is of great interest to a much larger section of society. Everyone may potentially benefit from the fruits of stem cell research, including hES cell research: all citizens who can become patients at some point in their lives, the research community, the pharmaceutical and biotechnology industry, politicians and many more. All of us are stakeholders in stem cell research. This has remarkable consequences for the course of the debate and, consequently, for stem cell policymaking. Pro-life US senator Bill Frist said in a recent speech: "if your daughter has diabetes, if your father has Parkinson's, if your sister has a spinal cord injury, your views will be swayed more powerfully than you can imagine by the hope that a cure will be found in those magnificent cells, recently discovered, that today originate only in an embryo."[4] Swaying views may not only be found on the individual level, but also, and subsequently, on the level of public policymaking.

Most countries, including those with restrictive regulations with regard to embryo protection in other contexts, do not want to block hES cell research because of the potential health benefits and the contribution to scientific progress it is believed to represent. They want at least some hES cell research to proceed, albeit under strict restrictions. The difficulty of developing such a 'permissive but very restrictive' stem cell policy not only lies in doing this without violating the spirit of existing regulations, as pointed out before, but also in justifying such policy in a pluralistic society where people are deeply and morally divided on the issue of embryo protection. Lastly, but by no means least, are the difficulties generated by the scientific uncertainty as to when the potential of hES cell research will be realised, if it will ever be. These quandaries form the major stumbling block in hES cell policymaking.

Most countries have tried to deal with these quandaries by adopting an 'intermediate position' on hES cell research, in the hope that a 'happy medium' can be achieved between the two polar positions in the hES cell debate: those who radically oppose any use of hES cells for research and those who think embryos, regardless of their origins, may be used to obtain stem cells. This intermediate view has two main variants, within which there can again be variations. These moral positions correspond with varying legal and regulatory approaches. The principal aim of these compromise attempts is to reach broad consensus on the issue of hES cell research, in order to develop regulations and legislations that permit the country and its citizens to enjoy the benefits of hES cell research without engaging in certain types of research that are deemed immoral by some in society.

Apart from adopting one of the versions of the intermediate position, another avenue has increasingly been explored in the hope of finding a compromise to overcome the major stumbling block in hES cell policy making. As Leon Kass, former Chair of the US President's Council of Bioethics, has pointed out, if a way could be found to derive hES cell lines without creating and destroying human embryos, a good deal of the ethical controversy in hES cell research would subside.[5] This has led to an increased trend to develop seemingly neutral scientific solutions, which claim to provide a method for obtaining hES cells without killing embryos, in order to find a way around the ethical dilemma in hES cell research.

In our pluralistic, morally divided societies, we have reason to believe that both types of compromise attempts will become an increasing trend over the coming years, hence the great importance of making them the subject of a broad scholarly debate.

2. OBJECTIVES, RESEARCH QUESTIONS AND METHOD

These compromise attempts, either by adopting some intermediate position or by developing a seemingly neutral scientific solution, will be the primary focus of my investigation. My focus on the issue of generating and killing embryos to obtain stem cells does not reflect the view that the other ethical issues raised by stem cell research are less important. I have opted to deal with this issue because it constitutes the principal stumbling block in stem cell research and stem cell policymaking. It will become clear throughout my dissertation and towards my conclusion that the other issues are of equal or of even greater importance than the issue of the moral status of the embryo, and therefore should be accorded more attention in the debate than has thus far been the case.

The objective of this dissertation is to investigate some of the most important implications of various compromise attempts in the hES cell debate, as well as their value as an ethical basis for science policy in pluralistic, morally divided societies. I hope that by this investigation and the discussion of the issues it raises, I can convey the importance of identifying, analysing and clarifying the ethical basis of compromise attempts as an important step in the evaluation of their political legitimacy. I thus wish to contribute to the broader debate about how and to which extent ethical positions should be integrated in science policy in a pluralistic and morally divided democracy.

The following two research questions are addressed to meet this objective and will be a continuing thread throughout my dissertation:

1. Are these compromises grounded in a well-argued ethical position?
2. Do these compromises succeed in their aim, that is, finding a 'happy medium' that allows some hES cell research to proceed, whilst respecting diverse views on the sensitive issue of the moral status of the embryo and without harming general interests of the public and violating important, widely shared principles and values in democratic societies?

To address these questions I will first identify the main compromise positions in the hES cell debate, as well as the possible groups of people for which these are intended. Rather than re-entering the vast debate on the moral status of the embryo, I will concentrate on the key arguments underlying the various compromises as well as on the arguments of their possible target groups. These arguments are expressed in statements, in literature as well as during conferences or media performances. I have called these arguments and what they stand for their 'professed beliefs'. To analyse and evaluate the moral positions in question which is relevant to the first research question, we need to critically analyse these professed beliefs. A central claim in my dissertation, however, will be that we should not only identify and examine people's professed beliefs, but also, and most importantly, what I have cal-

led their 'revealed beliefs', that is, what may be their actual beliefs and the morality they accept, as revealed through their acts and omissions. What is often forgotten or neglected in the stem cell debate is that very often there is a difference between what people *say* that they believe and what they *actually* believe. To succeed in what they aim for, that is, enabling 'permissive but restrictive' hES cell policy that does not offend some people's fundamental views on the moral status of the embryo, compromises should be directed at these people's revealed beliefs. Consequently, only by including the latter in our analysis can we assess the legitimacy of the compromises in the hES cell debate and whether they are to be effective at all in stem cell policymaking, which is relevant to the second research question.

This approach clearly has its limitations, as there is no well-defined or exact method to identify people's revealed beliefs, and we can never be certain whether they actually are their revealed beliefs, or whether their actions or omissions merely stem from weakness of will or out of ignorance. I am aware of these limitations. Nevertheless, when somebody *claims* to be acting from moral conviction, he must advance convincing arguments in support of such claim and these arguments must meet the minimum standards of evidence and argument. These arguments will also be embedded in a general moral principle or theory.[6] If one *claims* to act from moral conviction, one must act consistently with this theory or principle in other areas of life for this claim to be taken seriously. There is nothing wrong with temporal inconsistency, as it is a condition for moral development. If we are sincere, however, we should re-establish harmony between the beliefs we profess and our acts and omissions. This should be done on the basis of moral reflection and good arguments. This approach also encompasses the idea that, not only we should strive at maximum consistency between our professed and revealed beliefs, but also that our ethical beliefs should be revisable in the light of an understanding of, and critical reflection on our acts and omissions. If, for instance, certain practices are widely performed and accepted in most societies, this should also affect our picture of what kinds of actions are good or bad (although this is, of course, not a sufficient criterion). Principles should not be taken for granted. There should be a two-way interaction. Principles themselves, or their scope, may need to be reviewed in view of the morality we accept, which is revealed through our actions and omissions in responses on practical problems.

In order to deal with the second research question it will also be essential to investigate the implications of adopting these compromises as the ethical basis of a particular policy for accelerating or slowing down current and future stem cell research, as well as the implications for the protection of general interests of the public (e.g. the protection of public health) and widely accepted values in democratic societies (e.g. freedom of research).

3. STRUCTURE OF THE DISSERTATION

CHAPTER I: SCIENTIFIC BACKGROUND

Chapter I provides a summary of the science and the current state of the art of stem cell research. This

is not only essential to understanding what follows in the succeeding chapters, but is also intended to point out the scientific uncertainties underlying the ethical debate.

CHAPTER II: THE INTERMEDIATE POSITION IN THE HUMAN EMBRYONIC STEM CELL DEBATE

In Chapter II, I will examine the two main versions of the intermediate position in the hES cell debate: the 'use-derivation distinction' and the 'discarded-created distinction'.

Paper 1 deals with the use-derivation distinction. Defenders of this position make a moral distinction between *using* hES cells and *deriving* hES cells. Using hES cells is considered acceptable, whereas their derivation is deemed unethical because it involves killing human embryos. Stem cell policy in the United States and Germany is based on the use-derivation distinction.

Paper 2 examines the second variant of the intermediate position: the discarded-created distinction. 'Discarded' refers to embryos left over from fertility treatments and not wanted anymore for procreative purposes, either by their conceivers or by adoptive parents. They will be discarded if not used for research purposes. 'Created' refers to embryos created solely for the purpose of research, either by in vitro fertilization (IVF) or by somatic cell nuclear transfer (cloning). Defenders of the discarded-created distinction accept the use and derivation of stem cells from spare IVF embryos but oppose the creation of embryos solely for these purposes. Most European legislations have adopted this position.

A first aim of this chapter is to investigate whether both versions of the intermediate position are based on a well-argued ethical position. To do this, I will identify and analyse the ethical arguments underlying these compromises. A second aim is to assess the effectiveness of these compromises. To achieve this goal, I will identify the possible audiences these compromises are aimed at. I will then identify what may be their revealed beliefs, by investigating inconsistencies between their professed beliefs and the practices they accept or support. Taking into account these revealed beliefs, I will examine whether these compromises succeed in what they aim for. This will lead to the conclusion that these compromises cannot serve as a solid ethical basis for justifying restrictions on hES cell research. People who take the compromise position *either* simply do not believe the beliefs they profess, because of what they allow to be done or do themselves; *or* if they do mean what they say, they should follow through and be consistent in their actions/omissions and the practices they accept.

CHAPTER III: THE ROLE OF SCIENCE IN THE HUMAN EMBRYONIC STEM CELL DEBATE

The most controversial ethical issues concerning the generation and use of hES cells would be bypassed if it became technically possible to produce cells equivalent to hES cells, without creating and killing human embryos. This has led to an increased trend to develop seemingly neutral scientific solutions to find a way around the ethical dilemma in hES cell research. In this chapter I will deal with some of these scientific solutions and investigate to what extent and in which way they can contri-

bute to the ethical debate on hES cell research, and, subsequently, stem cell policymaking.
Paper 3 discusses two such solutions recently proposed to the US President's Council on Bioethics. Again, a central aim will be to identify the possible target groups for these compromises as well as to investigate whether these people really need the compromises. To find an answer to this question, I will, as in the previous chapter, consider their professed, but especially their revealed beliefs about how much protection embryos should get and under which conditions. This will lead to an evaluation of the effectiveness of the scientific solutions to overcome the major stumbling block in the hES cell debate.

As we will see throughout this chapter, these scientific proposals raise a very important issue that has long been neglected in the hES cell debate, namely the issue as to whether some of the embryo-like novelties developed for research can properly be called embryos. New techniques of embryo manipulation and the possibility to aggregate and disaggregate its cells have complicated the issue of how to define an embryo, and what exactly constitutes its value. This question already became more complex with the introduction of IVF, when the embryo's further development into a fetus and a baby became dependent on human intervention, namely placing it in a woman's uterus. This raised the issue of whether to accord equivalent moral status to the embryo *in vitro* and *in vivo*. Other types of embryo or embryo-like entities have raised the same question, for example those generated in a way other than 'normal' fertilisation by an egg and sperm (e.g. cloned 'embryos'). We may not, however, need to look further than within the 'normal embryo' itself to realise the complexity of this question. Ronald Cole-Turner, in his recent book, asks whether if in the future hES cells could be turned into human embryos, they would be regarded as the moral equivalent of embryos, and whether we would have to regard their descendants - the stem cells -as potential persons.[7] **Paper 4** aims at finding an answer to this question. Many people believe that an embryo must be protected as if it is a human person because it is a human organism with the 'inherent potential' to become a human person. It will be argued that current experimental evidence shows it is likely that hES cells, when given the appropriate environment and biological signals, will form into a normal fetus. As such, there is no difference between the 'inherent potential' of an embryo *in vitro* or a hES cell to form a person. I will examine the implications of this finding for the inherent potential argument against hES cell research and the consequences for the use-derivation distinction as an ethical basis for stem cell policy. I will argue that the inherent potential argument is applied inconsistently by opponents of hES cell research, and that because it can be used to both oppose and justify hES cell research it is an inadequate ethical basis for stem cell policy.

CHAPTER IV: THE MORAL IMPERATIVE TO CONDUCT HUMAN STEM CELL RESEARCH

In Chapter IV, I will discuss two possible applications of stem cell research that hold great potential for alleviating human suffering.

Paper 5 will deal with the issue of using pre-implantation HLA typing to have a tissue-matched child that can serve as a haematopoietic stem cell donor to save a loved one's life. This is generally known as the creation of 'saviour siblings'. Haematopoietic stem cells are found in the umbilical cord blood, bone marrow and peripheral blood (as will be explained in Chapter I). Despite recent promising results of using stem cells from the umbilical cord blood of so called saviour siblings for curing patients with blood diseases and certain types of cancer, this method has been met with much opposition. Unlike in hES cell research, it is not the *source* of the stem cells - the umbilical cord - that causes controversy, but concerns related to the risks of preimplantation genetic diagnosis (PGD) for the child to be born, the intention to have a donor child, the limits that should be placed on what cells or organs can be used from the child and whether the recipient can be someone other than a sibling. These and other issues will be addressed in paper 5. The main reason that I have opted for an application that is not directly related to hES cell research is to demonstrate that the same arguments and reasons for conducting and supporting the research can be applied to other types of stem cell research (and all important scientific research), and are not restricted to hES cell research.

The subject of **Paper 6** is cloning for research and therapy. Although cloning research is still in its infancy, it may one day give us the possibility to produce 'patient matched' tissue to repair damaged organs like the heart and brain, which have no capacity for regeneration. It may also provide a useful cellular model system for increasing scientific understanding of mechanisms involved in human development and disease. The starting point of this discussion will be the United Nations Declaration on Human Cloning (March 2005), which calls upon all Member States to prohibit all forms of human cloning.

Cloning and the use of pre-implantation HLA-typing to create tissue-matched stem cell donors are only two of the possible applications of stem cell research. I have selected these applications not only because they have caused a lot of controversy, but also because, if they are allowed and supported, their impact on medicine may be enormous in the case of cloning and immediate in the case of Preimplantation HLA-typing. Moreover, by dealing with these issues I wish to stress that apart from the issue of the moral status of the embryo, there are other ethical issues of substance that should be accorded more attention in the stem cell debate. I will use a consequentialist approach and depart from the view that an embryo has no significant moral status.

The principal aim of this chapter is to investigate why these applications of stem cell research have caused so much controversy, and whether the justifications for blocking them can hold true and can serve as an ethical basis for stem cell policy. To do this, I will first investigate the 'state of affairs' and the potential benefits of both types of stem cell research, and then determine whether there are good reasons to pursue the research and use the therapies. I will identify the main arguments of the opponents and investigate their ethical scrutiny. This will lead to the conclusion that these arguments are not strong enough to justify a ban or severe restrictions on these applications and the preceding

research. The conclusion will also outline that there are good reasons for not only allowing the research and its applications, but also positively supporting it through permissive legislation and generous funding.

CHAPTER V: CONTENTIOUS MORAL ISSUES AND STEM CELL POLICY

The aim of the final chapter is to investigate in what way and to what extent the ethical issues raised by stem cell research can or should be integrated in stem cell policies of pluralistically and morally divided democracies. It should be noted that different ethical issues will be integrated in different ways in various countries, as each country has its own cultural and legal context. It is, however, beyond the scope of this dissertation to investigate the determinants of each country's stem cell policy. Rather, I will study one case and use it to question the activity of developing compromises and the source of their political legitimacy. This analysis and the method used can then be used to investigate the ethical basis of stem cell policy (or science policy in general) in other countries.

Paper 7 will deal with current US stem cell policy, that is, stem cell policy as developed by the Bush Administration. The US presents an interesting case because of its extremes. On the one hand the US is a world leader in biomedical research and the government generally supports such research generously. On the other hand, the US is a nation where religious groups have powerful influence on public policy, including science policy, and lobby against any practice that they believe goes against their religious values. Another, strongly related, reason why the US is an interesting case is that there is a sharp dichotomy between regulation of federally funded and non-federally funded research and practices. In the US, research in the private sector is restricted only by state laws prohibiting embryo research. In states that have no laws against it, privately funded embryo research is essentially unregulated.

The aim of this paper is to investigate the current US government's approach to the federal funding of important research that is deemed unethical by some Americans. To do this, I will first analyse the moral grounds of this approach. I will then examine the actual and possible consequences of denying federal funding for hES cell research for the general interests of the American citizens and for widely accepted democratic values. This will lead to the first interim conclusion that President Bush's stem cell policy unjustly restrains scientific freedom merely on the basis of a highly contested value held by one particular group in society. In the second part of the paper, I will analyse the moral grounds of the compromise on which US stem cell policy is based and through an analogy, examine the value of the compromise by questioning possible inconsistencies between values, practices and regulations in the US. This will lead to the conclusion that the ethical compromise position on which US policy is grounded does not succeed in its aim, as it is not radical enough. Both intermediate conclusions will lead to the final conclusion that the compromise is not a valid ethical basis for stem cell policy.

Paper 8 presents an 'advance directive to protect embryos' so as to offer those who think hES cell

research is immoral, the opportunity to ensure in advance that they do not openly or inadvertently benefit from therapies developed through research that they consider evil, when it is possible for them to avoid it. If they are sincere about the arguments and principles they profess, we would expect them to make use of this opportunity offered to them. If they do not accept this offer, then this casts serious doubt about the validity of their arguments. It is very unlikely that opponents of hES cell research, when their own hour of need arrives will renounce the benefits of hES cell research. The advance directive is meant to dramatise the consequences of consistently holding a particular moral view and to stimulate discussion about how the hES cell debate should proceed.

Finally, a concluding paper is devoted to a brief summary of the overall conclusions with respect to our research questions and objectives, as well as the implications for future research.

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CHAPTER I
SCIENTIFIC BACKGROUND

1. STEM CELLS

Stem cells are 'unspecialised' or 'undifferentiated' cells, which means that they are immature cells that have not yet been directed to become a specialized cell with a specific function (e.g. a blood pumping heart cell). Stem cells have two unique characteristics:

(1) The capacity for unlimited or prolonged self-renewal
(2) The capacity to differentiate into at least one type of differentiated or specialised cell.[1]

2. HUMAN STEM CELL RESEARCH

Human stem cell research is the study of human stem cells *in vitro* and *in vivo*. Stem cells are regarded by many as the holy grail of medicine. Harold Varmus, former director of the National Institutes of Health (NIH) in the US, said with regard to stem cell research that "there is almost no realm in medicine that might not be touched by this innovation."[2]

This is not an exaggeration as the unique capacities of stem cells - self-renewal and differentiation potential - make them not only indispensable as building blocks for human development, but also invaluable tools in regenerative medicine. If an organ or tissue is diseased, it is not the whole organ or tissue that is damaged but its individual cells. Stem cells could serve as an inexhaustible source of replacement cells to regenerate diseased or damaged organs and tissues. Stem cells could, for example, be induced to differentiate into cardiomyocytes to replace damaged heart tissue, insulin producing _-cells for transplantation into the pancreas of diabetes patients, or dopamine producing cells for treatment of Parkinson's disease. In the future, it may even be possible to generate whole organs or tissues from stem cells.[3] Stem cells hold the promise of overcoming the problem of the shortage of suitable donor organs and tissues for transplantation. Their capacity for self-renewal and their differentiation potential make stem cells also invaluable for the study of basic and applied human biology (see below).

However, not all types of stem cells possess both capacities to the same extent. Not all stem cells have the same capacity for self-renewal. Neither do they all have the same differentiation potential.

3. CLASSIFICATION OF STEM CELLS ACCORDING TO THEIR DIFFERENTIATION POTENTIAL

With regard to their differentiation potential or potency, stem cells can be classified into three groups: totipotent, pluripotent and multipotent stem cells. As we will see later, the concept of stem cell potency is of crucial importance in 'the stem cell debate'.

Stem cell potency is best described in the context of normal human development.

3.1. Totipotent stem cells

In our earliest stages of development our cells are *totipotent*. Following fertilisation of an egg by a sperm the resulting entity - the zygote - undergoes cell division to form the two-cell stage. Subsequent cell division events result in the increase in cell numbers over a period of days until the morula is formed, consisting of eight cells. Up to this point the cells within the embryo can be considered *totipotent*. Totipotency refers to the capability of a cell to make all embryonic (3 germ layers: ectoderm, endoderm and mesoderm) and all extraembryonic (which generate the placenta and supporting tissues) cells required for human development.

This means that, in theory, any one of the cells up to the morula stage, if placed into a uterus, is capable of forming a human. (Due to ethical issues, however, this has not yet been demonstrated in humans).

3.2. Pluripotent stem cells

The morula gives rise to the blastocyst (50-130 cells - day 5 after fertilisation), which consists of two distinct cell types, the inner cell mass (ICM) and the trophectoderm. Trophectoderm cells, which form the outer layer of the blastocyst, give rise to the placenta and other tissues to support fetal development in the uterus. The cells of the ICM and its derivative, the epiblast, give rise to all embryonic cells as well as to primordial germ cells (the precursors of eggs and sperm). In other words, the ICM gives rise to the embryo proper. Because ICM cells can give rise to virtually all of the approximately 200 different cell types in the human body, but only to some cell types of the placenta and supporting tissues necessary for development of the organism in the uterus, ICM cells are considered *pluripotent*.[4] These pluripotent cells are only present for a very short time (approximately 5 to 7 days), with exception of the germ cells which retain pluripotentiality until midgestation.

3.3. Multipotent stem cells

As the blastocyst continues its development, cells undergo further specialization. Stem cells, when they divide, generate other stem cells as well as daughter cells that undergo further differentiation. The latter are progenitor cells and are commonly referred to as transit amplifying cells. They divide finitely and function to increase the number of cells derived from a single stem cell division. These cells have been extensively studied in the haematopoietic (blood-forming) system, where the cells become increasingly restricted with each cell division and subsequently become a fully differentiated cell type. Progenitor cells cannot self-renew infinitely and, therefore, are not true stem cells. They can be found in fetal and adult bodies.

Stem cells are the building blocks of the embryo, but they also persist throughout our whole lives. They play an important role in repairing organs and tissues (skin repairs itself after injury and a liver can regenerate up to 50% of its mass within weeks[5]), and in replenishing our supply of certain cells,

such as blood cells (our red blood cells are replaced at a rate of 350 million per minute), throughout life. Most stem cells found in humans after birth are *multipotent*. Multipotent stem cells can give rise to a limited number of different cell types, typically the cell type from the organ or tissue, or the area in the body they originate from. For instance, skin stem cells give rise to epidermal cells, sebaceous cells and hair follicles; haematopoietic stem cells give rise to all the blood cells; and neural stem cells give rise to neurons, astrocytes, and oligodendrocytes.[6]

The most promising stem cells to work with are pluripotent stem cells, as they can differentiate into virtually any mature cell in the body.

Stem cell potency

- Totipotent: capacity to differentiate into all extraembryonic, embryonic and adult cell types.
- Pluripotent: capacity to differentiate into some extraembryonic and all embryonic and adult cell types.
- Multipotent: capacity to give rise to some adult cell types.

A problem with classifying stem cells according to their differentiation potential is that this potentiality depends on the differentiation context, for example, the stem cell niche *in vivo*[7] or the content of the Petri dish in which stem cells are cultured *in vitro*.[8] This is relevant to the ethical debate, as it may indicate that arguments for embryo-protection based on differentiation potential may be of limited relevance. This also has implications for regulations and legislations with regard to embryo protection that are based on differentiation potential, such as the German Embryo Protection Act of 1990. I will investigate this issue in Chapter III.

4. CLASSIFICATION OF STEM CELLS ACCORDING TO THEIR ORIGIN

Another way of classifying stem cells is according to the source they were derived from. Stem cells may be derived from fluids and tissues from humans from the moment of conception until after death. Generally, stem cells are classified as: adult, fetal or embryonic stem cells. More recently, umbilical cord blood stem cells, sometimes called 'neonatal' stem cells, have been added as a separate category. As we will see in paper 3, classification of stem cells according to their origin raises some difficulties as well. As scientists continue to look for new stem cell sources, it is not always clear as to which category stem cells obtained from these alternative sources belong, or whether they belong to any one of them. It should also be noted that this classification does not necessarily reflect the stem cells' differentiation potential, as is sometimes assumed. It is often not 100% clear how versatile the cells in question are. Sometimes stem cells are classified in only two groups: embryonic and somatic stem

cells; the latter referring to all cells other than those originating from embryos.

The use of different definitions and terminology, in scientific and other literature, is often confusing. It is to be expected that as stem cell research progresses, more accurate nomenclature will develop.

At the time of writing, the following categories are most commonly used:

4.1. Adult stem cells

Adult stem cells can be found in many tissues and organs in humans after birth throughout their whole life, primarily in the bone marrow, but also in peripheral and cord blood, the brain, spinal cord, gum tissue, epithelia of the skin and digestive system, cornea, retina, liver, teeth and many more.
It has been known for a long time that some adult tissues contain stem cells that can replenish the supply of cells in that tissue. This knowledge has been used to develop treatments, which have become routine now, such as skin repair in the case of burns, and bone marrow transplantation for treating certain cancers and blood disorders. Bone marrow transplantation, for example, involves the intravenous injection of autologous or allogeneic haematopoietic stem cells into a patient whose blood cells (including the cancer cells) have been destroyed, for example, by high doses of chemotherapy and/or irradiation. The transplanted stem cells 'home' into the bone marrow of the patient where they start to produce all the blood cells (a new cancer-free immune system).
It has usually been assumed that adult stem cells are multipotent, that is, only capable of developing into cell types of the associated organ or area of the body. Over the past six years, studies have suggested that some adult stem cells have greater plasticity than previously believed, especially stem cells found in the bone marrow (haematopoietic stem cells, mesenchymal stem cells and endothelial progenitor cells[9]). In January 2002, Catherine Verfaillie of the University of Minnesota reported the discovery of multipotent adult progenitor cells (MAPCs) isolated from human bone marrow. These adult stem cells were demonstrated to be capable of prolonged self-renewal and of giving rise to other tissues than their tissue of origin, including muscle, cartilage, bone, liver and different types of neurons and brain cells. [10]

Verfaillie's results caused much excitement. "Ultimate stem cell discovered", was the heading of a news article in the *New Scientist*.[11] *Nature* wrote: "stem cell hopes double".[12] It was generally accepted that only stem cells from embryonic origin were pluripotent. If it could be proven that some adult stem cells had the same potential as embryonic stem cells, this would overcome many of the ethical and political hurdles in stem cell research and policy making. Embryonic stem cell research, which is very controversial because it involves the destruction of embryos, would then become superfluous to reach the intended therapeutic goals. The main ethical issues in the stem cell debate would be resolved.

Other studies seemed to confirm the plasticity of adult stem cells. Adult mouse neural stem cells have been found to differentiate into skeletal muscle, heart, lung, blood and skin after transplantation.[13]

British researchers reported that human skin cells can turn into neurons.[14] Studies in mice have suggested that human bone marrow stem cells and stem cells from the umbilical cord blood can be transformed into neural cells, and could possibly be used for brain repair.[15]

Adult stem cell plasticity, however, has been called into question, in part because, (1) most of the studies that have demonstrated adult stem cell plasticity have not been confirmed by independent research teams, (2) because of the low frequency at with which apparent cell transdifferentiation occurs, and (3) because most studies cannot prove that the plasticity is the result of a single stem cell that differentiates into more than one functionally characterized lineages.[16] It has, for example, been shown that the plasticity observed is due to the stem cells fusing with a differentiated cell and reprogramming it to a more primitive state.[17] Although more than ten research teams have reported adult stem cell plasticity, without further evidence, the differentiation potential of adult stem cells remains controversial.[18]

Around 20 main types of adult stem cells have been discovered to date. Most of these cells are difficult to isolate. They are present in small numbers (in mouse bone marrow, only 1 in 10,000 cells is a stem cell, and in humans the ratio may even be less) and often hard, if not impossible to harvest from the patient's organs and tissues, for example, the heart, the brain or the pancreas. In most tissues there is no predictable location for stem cells, and techniques to identify stem cells are not efficient. Adult stem cells are slow and labour-intensive to grow in the laboratory.[19] It is also not clear to which extent adult stem cells have the potential for self-renewal. If they have restricted potential for self-renewal, this will have negative implications for therapeutic applications. Effective transplantation requires sufficient amounts of stem cells. It is also suspected that the number of adult stem cells decreases with age, and some say it may be problematic to use adult stem cells, for example, from a person over fifty, because these cells will have accumulated damages of aging, including genetic mutations, which could lead to cancer or other age-related diseases. However, a study has shown that intestinal stem cells retain an original DNA template strand for their whole existence.[20] If true in all stem cells this means that the stem cells will not have accumulated damage due to ageing.

Adult stem cells have one enormous advantage over stem cells from most other sources: they can be harvested from the patient, ruling out the possibility of immune rejection after transplantation. Immune rejection occurs when the recipient's body fails to accept a transplanted tissue or organ because it is recognised as foreign, and consequently attempts to destroy it. It is the most serious problem faced in surgery involving organ or tissue transplants. Because adult stem cells can be used for autologous transplantation, which refers to a graft in which the donor and recipient area are in the same individual, immunorejection can be avoided. Another advantage of adult stem cells stems from their limited ability to proliferate, which would reduce the risk of malignancy in therapeutic use.[21]
Instead of isolating/culturing/replacing adult stem cells, it has been suggested that adult stem cells present in the body could be triggered to migrate to and regenerate the damaged body-part. This would

give us the capacity to re-grow our own tissues and organs, just like zebra fish can re-grow entire limbs and organs.[22] Much research, mainly on the roles played by chemical signals that lead stem cells to damaged body parts, is still required to reach this goal.

4.2 Neonatal stem cells from the umbilical cord blood

Of all adult stem cells that have been identified, haematopoietic stem cells are the most versatile, and most easily to obtain. Umbilical cord blood (UCB) is a rich source of haematopoietic stem cells. UCB stem cells are sometimes categorized as adult stem cells. Others refer to them as fetal cells. More recently, they have been categorised as 'neonatal stem cells'. The harvesting of stem cells from UCB has been practiced for some years, in order to obtain haematopoietic stem cells as an alternative for bone marrow transplantation. UCB stem cells are collected after delivery of the baby. Cord blood is usually considered as a discarded product once the baby is born. The first successful transplantation of UCB stem cells was reported by Gluckman and Boxmeyer in 1989, for the treatment of a patient with Fanconi anemia, an inherited form of anemia which leads to bone marrow failure.[23] The donor was his HLA-identical sister who was known by pre-natal diagnosis to be HLA[24] identical and not affected by the Fanconi mutation. The success of a transplant is dependent on how well the HLA-types of the donor and recipient match. In the past, parents of a sick child in need of a UCB transplant have planned pregnancy in the hope to obtain HLA-matched UCB stem cells after delivery. More recently, pre-implantation genetic diagnosis (PGD) has been proposed as a method for selecting HLA-matched embryos in order to create a tissue matched child that can serve as a stem cell donor. After delivery of the HLA-matched baby, UCB cells can be collected and cryopreserved for transplantation to the sick sibling. There have been some successful so called 'saviour sibling' cases, most recently the 'Whitaker case'. Charlie Whitaker has recently been said to be cured of Diamond Blackfan anaemia - a blood condition, characterized by an inability to produce red blood cells, caused by a failure within the bone marrow. The six-year old boy received a UCB transplant obtained after delivery of his little brother, who was born after pre-implantation HLA-typing. In paper 5, I will discuss the ethics of using pre-implantation HLA-typing to have a child that can serve as a haematopoietic stem cell donor to save a loved one's life.

Worldwide, efforts are being undertaken to collect UCB cells and store them in freezers for later use in transplantation. The first UCB bank was founded in 1993 in New York (New York Blood Center, NYBC). Since then, large-scale UCB-banking has been established worldwide. To date, more than 100,000 UCB units are registered and available for transplantation in more than 50 banks worldwide and more than 3000 patients, most of which are children, have received UCB stem cells from these banks.[25]

UCB banks can be private or public. Private UCB banks store UCB for the family's own use. Parents have to pay for storage of the UCB of their child. The idea is that should the child or another family member at some point in his/her life need a haematopoietic stem cell transplant, these cells will be immediately available, and will (very likely) be an HLA-match. Public UCB banks collect UCB after

consent of the mother. Storage is free, but the UCB is intended for any patient in need of a UCB transplant. It is not reserved for the family's private use. Doctors all over the world search the National Marrow Donor Program Registry of donors and cord blood units to find a match for their patients who need a transplant.

There is a growing consensus among scientists on the great value of UCB stem cells for transplantation. They are easy to obtain and have been shown to be more versatile than other adult stem cells. Kogler and colleagues, for example, identified human adult stem cells from the umbilical cord blood with intrinsic pluripotent differentiation potential.[26] In South-Korea, a medical company plans to open the world's first hospital exclusively providing UCB treatment by 2007.[27] UCB has several advantages over bone marrow transplantation: the large donor pool, the low incidence of viral infection at birth, the low incidence of graft versus host disease due to the immune immaturity of the newborn (UCB stem cells are less mature than haematopoietic stem cells found in the bone marrow), the increased speed of availability in stem cell banks,[28] and the less costly use.[29] One disadvantage is that the number of UCB stem cells in one umbilical cord is too small to treat an adult. However, research is being pursued to overcome this problem and adults have been successfully treated with UCB stem cells.[30]

4.3. Fetal stem cells

In 1998, John Gearhart and his team at the Johns Hopkins University School of Medicine was the first to establish pluripotent stem cells from human fetuses or post-implantation embryos.[31] His team isolated and cultured primordial germ cells (precursors of eggs and sperm) from the gonadal ridges and mesenteries of 5 to 9 week fetuses obtained by therapeutic abortion. The embryonic germ (EG) cells thus obtained have been shown to give rise to cell types of the three germ layers, and can thus be called pluripotent. EG cells represent important in vitro models for cells and developmental biology.[32] However, because pregnancy terminations happen at various times EG cells can be difficult to harvest. There is only a limited time span during which EG cells can be obtained - within the first 8 to 9 weeks after conception. Moreover, EG cells have limited proliferation capacity. Despite these disadvantages, research results suggest EG cells could be therapeutically useful. Human EG cell derivatives have lead to regenerative repair when implanted into rat brains and spinal cords, which offers hope for treatments for neurodegenerative diseases, such as Parkinson's disease.[33]

Apart from primordial germ cells, two other sources of fetal stem cells have been investigated: trophoblast stem cells and fetal tissue stem cells.[34] Stem cells derived from human fetal tissue have shown long-term promise in treating strokes in rats. [35]

4.4. Embryonic stem cells

The most versatile type of stem cell is the embryonic stem (ES) cell. ES cells were first isolated in mice in 1981[36] and in humans in 1998.[37] At present, human embryonic stem (hES) cells are derived from the ICM/epiblast of the blastocyst.[38] Through the derivation process the embryo is 'dismantled' and impeded in its further development to a human. Some say the embryo is 'killed' or 'destroyed' through the derivation process.

In the laboratory, hES cells can grow indefinitely in the unspecialised state while retaining the ability to give rise to a wide range of body cells. They are pluripotent. Because of limitations on the type of experiments that can be done with hES cells has it been possible only in the mouse to demonstrate rigorously that hES cells can give rise to every tissue in the body. Injection of undifferentiated hES cells into immunodeficient mice results in growth of teratomas (non-malignant tumours), which contain cell types of all three germ layers, demonstrating their pluripotent nature. [39]

Many studies also have demonstrated the differentiation potential of hES cells *in vitro*. For instance, hES cells have been shown to give rise to neural progenitors,[40] to insulin-producing cells[41] and cardiomyocites,[42] and endothelial cells.[43] Recent findings suggest that it is also possible to generate *in vitro* germ cells from hES cells in a Petri dish.[44] If it can be demonstrated that these gamete-forming cells can become mature and are capable of functioning in fertilization and subsequent embryonic development, this would have enormous potential for infertility treatment, as well as for the shortage of eggs in therapeutic cloning.[45]

The pluripotentiality and their proliferation potential make hES cell powerful tools for research and therapy.

4.4.1. Medical Research

hES cells hold great promise for medical research. They would facilitate the study of early human development, and the underlying mechanisms regulating stem cell growth, migration, and differentiation. As techniques for making genetic modifications in hES cells have become available, hES cells become a powerful tool for functional genomics. They would provide powerful tools for learning about the function of certain genes and proteins, and their interactions with environmental factors. hES cells also make it possible to create cellular models of human diseases and to study gene function in a human cellular context.[46] Cellular models of human diseases also are of great importance for drugs screening and toxicity testing

4.4.2. Transplantation medicine

The promise of hES cells that causes most excitement is their potential use as an inexhaustible source of replacement cells for transplantation therapy. They could be used for treating many diseases and conditions for which currently no cure exist, including Parkinson's disease, diabetes, certain cancers, spinal cord injury, blind- and deafness, and many others.

Clinical use of stem cells is currently restricted to adult and UCB stem cells.

In the mouse, however, there is proof of concept for the use of ES cells to treat models of diabetes,[47] Parkinson's disease,[48] myocardial infarction,[49] spinal cord injury,[50] and a severe genetic immune disorder.[51]

Any therapeutic use of stem cells that is not derived from the patient has to overcome the problem of immune rejection. In the case of adult stem cells and UCB stem cells, the cells can be harvested from the patient. hEG and hES cells would normally be allogeneic cells, which means they have a genetic

identity different from that of the recipient, and will be rejected. To overcome the problem of immunorejection a number of solutions have been proposed,
including (1) immunosuppressive drugs for the recipient (which makes the patient more vulnerable to infections and cancers, and can even be lethal); (2) setting up stem cell banks with hES cells lines representing a wide spectrum of major histocompatibility complex (MHC) alleles (which raises issues about ownership and access). It should be noted that most of the existing hES cell lines have been in contact with mouse embryonic fibroblasts and, because of the risks associated with xenotransplants, are unlikely to be of any use in the clinic. Recent alternatives are the derivation of hES cells on feeder free layers[52] or on human feeder layers[53]; (3) the generation of universal donor lines in which the MHC genes could be genetically altered (raises issues related to gene therapy); (4) manipulation of T cell activity, and the use of combined transplant, which will replace the patient's haematopoietic and lymphoid systems with ES-cell derived cells, followed by engraftment of the target cell type derived from the same ES cells.[54] (5) The solution that has attracted most attention is the possibility to obtain hES cells that are genetically identical to the patient through somatic cell nuclear transfer (SCNT), or what has generally been called 'therapeutic cloning'.

4.4.3. Somatic cell nuclear transfer

Currently, the main source of hES cells are embryos left over from fertility treatment and donated after informed consent by their conceivers. Another possible source is embryos created by IVF with gametes donated solely for research purposes, so-called 'research embryos'. To overcome the problem of immunorejection, however, hES cells could be established from embryos cloned from body cells of the patient. In May 2005, Woo Suk Hwang and colleagues of Seoul National University reported that they had successfully cloned 31 human embryos and had produced 11 ES cell lines from these.[55] The cells were cloned from body cells from patients with diseases potentially amenable to stem cell therapy, including genetic disease, spinal cord injury and diabetes.

Cloning through somatic cell nuclear transfer (SCNT) involves taking the nucleus with the DNA code of a somatic cell and transferring it to an enucleated egg, which will then be activated and will start to divide, to form an early embryo. An embryo created through SCNT will be genetically identical to the donor of the cell nucleus (or nearly identical depending on the source of the mitochondrial DNA[56]). On February 24 1997, Scottish scientists announced that they had cloned Dolly the sheep using the SCNT technique.[57] She was the first mammal ever to be cloned using a fully differentiated adult (somatic) cell. Using SCNT to produce live offspring is often referred to as 'reproductive' cloning. In therapeutic cloning, the cloned embryo is not transferred to a uterus for further development, but is 'dismantled' to harvest hES cells that are genetically identical to the patient. Because the cells would come from the patient, as in Dr. Hwang's experiment, there would be no need for drugs to prevent rejection, which still cause inconveniences and can even be lethal. Cloning may give us one day the possibility to produce 'patient matched' tissue to repair damaged organs like the heart and brain, for stroke and heart attack, Parkinson's disease and many other diseases. Rideout and colleagues recently

reported the cure of a genetic disease using therapeutic cloning. [58] They created a mouse with the Severe Combined Immunodeficiency (commonly known as the "boy in the bubble disease"). They took cells from the tail, subjected these to the cloning process, established ES cells in which the gene was introduced to correct the genetic defect. These were introduced back into the mouse, curing the disease. This is dramatic proof of concept for therapeutic cloning in the mouse.

Cloning research is still in its infancy and much more research needs to be done, for example, to overcome the problem of using somatic cells of patients with inherited gene mutations. These will have to be corrected before the reprogrammed somatic cells are transplanted back into the patient.

Apart from its therapeutic potential, the value of cloning also lies in the possibility to create cellular models of human diseases, and the knowledge that can be gained from this in different research areas. Cloning could contribute to a better understanding of the genetic basis of human diseases and of the reprogramming faculty of human genes. In paper 6, I will go deeper into the technical aspects of cloning for research and therapy.

4.4.4. Challenges for hES cell research

Science of pluripotent hES cells is still in its infancy. Many technical issues remain to be solved.[59] More research is needed into the self-renewing capacity of hES cells, and into means to ensure stability of genotype, epigenetic status, and phenotypic properties of hES cells. hES cells need to be generated in pure form and in sufficient numbers to be therapeutically useful. Another challenge is to direct the differentiation of hES cells down a particular pathway to generate the desired cells that are restricted to specific developmental fates. In addition, a better understanding is required of what stem cell type to supply for treating a particular pathology, and how to deliver it. For instance, by simply injecting hES cells into the damaged body part, or by first coaxing them into progenitor cells or fully differentiated cells. Transplanted hES cell progeny may not function normally in organs and might retain tumorigenic potential, a characteristic of hES cells. As said before, the avoidance of immunological rejection remains one of the biggest challenges. There are numerous unanswered questions as to the control of ES cell growth and differentiation. ES cells have the potential to be tumorigenic, growing into teratomas and teratocarcinomas when injected into mice. Research is being done on this worldwide and progress is being made.[60] Recent research shows there may be infectious and other risks, such as occurred with BSE, of transplanting such tissue back to people, when it is grown on foreign culture material.[61]

4.5. Alternative sources of pluripotent stem cells

Because of the ethical controversy surrounding hES cell research, scientists have been looking for alternative sources of hES cells or cells with the same functional capacity that do not require the 'killing' of embryos, or, at least, only involve the killing of embryos that, according to some, have 'lesser' moral status, such as affected embryos or embryos that have a high risk of being affected[62] (embryos left-over from IVF and not suitable for transfer to the uterus[63] - it is not known yet if hES cell lines obtained from poorer quality embryos differ from hES cell lines from higher-quality embryos[64] - and embryos

left-over from PGD[65], which allow for the generation of disease-specific hES cell lines - however, the number is limited, with less than 200 a year being available in the UK[66]). Others proposals involve harvesting hES cells from organismically dead embryos[67] (embryos left-over from fertility treatment that have spontaneously died), parthenotes[68] (cleaving eggs that were activated without being fertilized by sperm), and biological artefacts[69] (including what I have called ANTities, see paper 3). It has not proved possible yet to derive hES cells from the parthenotes, but research is ongoing. The creation of biological artefacts is an untried method, and it is not clear whether hES cells or cells with the same functional capacity can be derived from these.[70]

Another proposal involves blastomere extraction from living 6 to 8-cells stage embryos and subsequent establishment of hES cells from one single blastomeres. Removal of a single cell at this stage of development should not endanger further development of the embryo. Strelchenko and colleagues have shown that ES cells can be derived from human embryos consisting of 8 to 24 cells.[71] However, in their experiment they disaggregated all the cells of the morula. It is not yet possible to reliably derive ES cell lines from a single cell extracted from an intact early embryo.
With regard to overcoming ethical and political issues, the ideal scenario for regenerative medicine would be to generate human pluripotent stem cells directly, that is, without first creating an embryo that must be 'killed' to derive stem cells. One such proposal is to generate patient-matched stem cells by reprogramming somatic cells, without using oocytes or creating new embryos. One way to do this is by fusing existing hES cells with somatic cells. The fusion causes the somatic cells to undergo genetic reprogramming to a pluripotent state. Eggan and his team at Harvard reprogrammed the gene expression of human fibroblast cells by using this technique. The resulting cells behaved like embryonic stem cells, and had an almost identical expression profile of that of normal embryonic cells.[72] It is hoped that this technique can one day serve as an alternative to cloning by SCNT, which requires embryo destruction and the use oocytes. Interestingly, the knowledge required for reprogramming somatic cells will be derived from preliminary research on hES cells, which were harvested from embryos solely created for the purpose of research. Another proposal to directly generate pluripotent stem cells has been called oocyte assisted reprogramming (OAR). OAR involves SCNT, but before the nucleus is transferred to an enucleated oocyte, the somatic nucleus or the cytoplasm of the oocyte would first be altered in such a way that the oocyte will reprogram the somatic nucleus to a pluripotent, but not a totipotent state (which would be an embryo).[73]
I will go deeper into scientific and ethical aspects of some of these alternative sources of human pluripotent stem cells in paper 3.

5. WHICH WAY FORWARD?

Although a great many scientists are committed to stem cell research worldwide and new discoveries and progress continue to be made, stem cell research is still largely in the experimental stages. There is as yet no consensus in the scientific community on the exact characteristics and the potential of the different types of stem cells. Before therapeutic applications can be realised, many technical hurdles

need to be overcome and many unanswered questions need to be resolved. Discussion on the relative advantages of each type of stem cell is on the present scientific agenda. At the time of writing, it is not known which line of research is the most promising for reaching the intended research and therapeutic goals. However, there is a growing consensus among scientists worldwide that all lines of stem cell research are promising. Embryonic, UCB and adult stem cells have different qualities and may be useful for different purposes. It has, for example, been said that adult stem cells will prove more suitable for particular therapies, such as to repair damaged liver tissue, while hES cells would offer most promise for treating heart conditions, Parkinson's disease and diabetes.[74] In some cases the best option may be combined adult and embryonic stem cell therapy.[75] Support has been expressed to investigate alternative sources of pluripotent stem cells, as long as this does not restrain the other lines of research. So rather than opting for one line of research, the ideal research strategy to reach the intended research goals seems to proceed with research on all types of stem cells.[76]

Milestones in ES cell research:

- 1981: Evans et al., *Nature*, establishment of mouse ES cells from the ICM of blastocysts
- 1996: Wilmut et al., *Nature*, reprogramming of somatic cells after nuclear transfer into enucleated eggs (birth of Dolly, the cloned sheep)
- 1998: Thomson et al., *Science*, establishment of hES cells, Shamblott et al., *Proc Natl Acad Sci U S A*, establishment of hEG cells.
- 2003: demonstration of germ-line development of ES cells in vitro
- 2004: Hwang et al., *Science*, establishment of hES cells from cloned embryos, using eggs from somatic cell donors with diseases amenable for stem cell therapy
- 2005: Hwang et al., *Science*, establishment of hES cells from embryos cloned from donor oocytes and patients with diseases amenable for stem cell therapy.

ACKNOWLEDGMENTS

I wish to express my gratitude to. Christopher Ward and. Peter Ponsaerts for very helpful comments and suggestions to improve this text and make it scientifically accurate.

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CHAPTER II
THE INTERMEDIATE POSITION IN THE HUMAN EMBRYONIC STEM CELL DEBATE

PAPER 1
THE USE-DERIVATION DISTINCTION

Adapted from:
Devolder, K. and Harris, J. Compromise and moral complicity in the embryonic stem cell debate. In: Athanassoulis, N, Ed. *Philosophical Reflections on Medical Ethics*. Palgrave MacMillan; 2005 Sep: 88-108

1. ABSTRACT

This paper deals with one version of the intermediate position in the human embryonic stem (hES) cell debate: the use-derivation distinction. Defenders of this position make a moral distinction between using hES cells on the one hand and their derivation on the other. Using hES cell is considered ethically acceptable but their derivation not, because it involves killing human embryos. We will argue that the use-derivation distinction cannot be sustained, and, therefore, cannot serve as an ethical basis for stem cell policy. The reasons are twofold: first, the separation between using and deriving hES cells cannot be guaranteed in practice. Consequently, support for using hES cells is acceptable only if the stem cell derivation process is acceptable. Secondly, those who claim the embryo should be protected as if it was a person are committed to a position even they do not uphold in their practices. Given that they are willing to treat the embryo as a mere means in other practices, and that hES cell research holds great potential to benefit many people, one cannot but conclude that hES cell research is permissible and, given its immense promise for alleviating human suffering, even obligatory.

2. STEM CELL RESEARCH

In September 2004, Italy's health minister Girolamo Sirchia hailed the successful treatment of a 5-year old boy with Thalassaemia, an inherited form of life-threatening anaemia. The therapy involved transplanting stem cells of the umbilical cord blood of the boy's newborn twin siblings. The Minister hoped to use this case to convince the Italian public of the potential of non-embryo-derived stem cells and to justify the contentious Italian law on assisted reproduction. However, soon after his 'triumph' it became known that the twin pregnancy was realised with IVF and the selection of embryos through PGD and HLA-typing in a hospital in Turkey, techniques which Sirchia considers as immoral and which are outlawed by the Italian government.[1]

Stem cells hold great promise for medicine. Because of their proliferation and differentiation capacities they are widely believed to represent the greatest promise for medicine in the twenty-first century. They could be used to treat a variety of diseases and conditions, including diabetes, Parkinson's disease, heart disease, spinal cord injuries, blindness, deafness and many types of cancer. Unlike current drugs, which mainly delay symptoms of diseases, stem cells may make it possible to replace damaged tissue or even whole organs. Their value extends beyond utility in cell therapy. Stem cells are also useful tools for fundamental research, mainly for gaining knowledge about early human development, cell division and differentiation mechanisms, gene and protein function, for developing drugs and toxicity testing, and for developing models of human diseases.[2] This immense promise gives powerful moral reasons for pursuing stem cell research.

At present there are three main lines of stem cell research:[3] (1) on stem cells originating from early *in vitro* embryos made available as surplus to those required for infertility treatments or especially created for research through IVF or nuclear transfer (embryonic stem cells); (2) on umbilical cord

blood-derived stem cells; (3) on stem cells originating from tissues or organs from fetuses or organisms after birth (fetal and adult stem cells). There is a growing consensus among scientists worldwide that all these lines of research are promising. Embryonic, cord blood, fetal and adult stem cells may have different qualities and might be useful for different purposes. In some cases the best option may be, for example, combined adult and embryonic stem cell therapy.[4] So rather than opting for one line of research, the ideal research strategy to reach the intended research goals would be to proceed with research on all types of stem cells.

However, human embryonic stem (hES) cell research which involves the 'destruction' of the embryo is opposed by those who regard the embryo as in some important sense 'one of us'. In the opinion of those who take this view, the embryo should never be used as a mere means, even if this could save millions of lives.[5] They advocate the legal prohibition of stem cell research or therapy that involves 'the killing' of human embryos. This approach may be summed up in the phrase 'the embryo is one of us', which entered the vocabulary of the moral status of the embryo via a leading Italian Catholic commentator. It has since become associated with this debate not only in the Italian context but more generally.[6]

3. STEM CELL POLICY

The fact that there are no cures as yet on the basis of hES cells can appear as an embarrassment for those seeking clear justification of hES cell research. This creates a situation in which tensions between ethics and politics are unavoidable and very visible. An argument that always surfaces in the stem cell debate and about which there is a broad consensus, is that there is no need to permit more ethically contentious ways of generating stem cell lines if the same benefits can be realised using less contentious stem cells.[7] It is sometimes referred to as the principle of subsidiarity[8] and it is closely bound up with the principles of proportionality and necessity, which require that any action should not go beyond what is necessary to achieve the objectives. The principle is referred to very often in reports and recommendations on stem cell research. The Belgian law on the Protection of the Embryo in Vitro, for example, states in Art.3 §6 that research on embryos is allowed if no other research method exists that is equally effective and in Art.4 §1 that the creation of embryos for research is forbidden except when the goal of the research project cannot be reached through research on supernumerary embryos. The US National Bioethics Advisory Commission wrote in its stem cell report of 1999 that "the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research".[9] The German Stem Cell Act stipulates that hES cell research shall not be conducted unless the scientific knowledge to be obtained cannot be expected to be gained by using cells other than hES cells.[10]

Those who use the principle that we have to opt for the least offensive moral approach assume that there exists a sort of hierarchy of the various methods of obtaining stem cells according to their ethical acceptability, on which the majority of people agree. Adult stem cells are placed at the top and stem

cells harvested from embryos created solely for research purposes at the bottom. In between there is a variety of intermediate positions. If the intended goals of stem cell research can be reached with stem cells from all the possible stem cell sources, then - following the argument - only the less controversial source should be used. The question as to whether this argument is valuable and useful in a bioethical context we leave out of consideration in this paper.[11] More important in this context is the fact that it actually serves as a guiding principle in political decisions about stem cell research. Consequently, if there was scientific certainty that adult stem cells were the most advantageous stem cells or as advantageous as hES cells to reach the intended goals, it is very likely that in many jurisdictions, policy-makers would legalise their use and would prohibit research with hES cells.

But, as already noticed, there is still scientific uncertainty about which line of research is the most promising for specific purposes. Many scientific publications have presented findings about the great potential of hES cells[12] and a majority of scientists claim that the best way to make scientific progress is to do research on all types of stem cells.[13] This presents many countries with difficult decisions about the regulation of hES cell research.

In a democracy it is always necessary to balance a wide range of interests and opinions. Most countries do not want to block hES cell research because of the potential health benefits and the contribution to scientific progress that stem cell research is believed to represent. For countries with restrictive laws with regard to the protection of embryos in the context of abortion, IVF and fetal tissue research, the problem is to justify certain forms of hES cell research without violating the spirit of these existing laws. These difficulties explain why the focus of the current stem cell debate is on the question whether hES cell research should be allowed - or federally funded[14] - or not, and, if so, which aspects and with which constraints. It is partly a re-ignition of the older debates, but there are differences that make the debate more complex, namely that hES cells can be cultured and proliferated in the laboratory on the one hand, and that spare embryos and embryos solely created for research can be used as a stem cell source on the other.

4. MORAL POSITIONS IN THE HUMAN EMBRYONIC STEM CELL DEBATE

Two polar moral positions can be distinguished in the hES cell debate. First, those who radically oppose research with stem cells obtained from human embryos. In their opinion, the embryo has the same moral status as a person and consequently, has to be (legally) protected as a person. They portray adult stem cell research and other research strategies as viable alternatives.[15]

Second, there is the viewpoint that young *in vitro* embryos, regardless of their origins, may be used for scientific research on the condition that the embryos used in the experimentations will not be implanted in the womb afterwards (unless the research has therapeutic value for the embryo and the

person that will result from it). The principal requirements regarding hES cell research are related to safety and control, proportionality, commercialisation and informed consent issues. In Europe, Belgium, the UK and Sweden (and to a certain extent the Netherlands) have regulations compatible with this viewpoint.[16]

Most countries adopt an 'intermediate view'. They search for a 'happy medium' between these two polar views. This middle position has two main variants: one based on the 'use-derivation distinction' and one on the 'discarded-created distinction'.[17] The first makes a moral distinction between the use of hES cells and their derivation from *in vitro* embryos; the second between the use of spare IVF embryos for research and the use of embryos solely created for research. Within these two positions there can again be variations. These moral positions correspond with varying legal approaches, from the prohibition of hES cell research to the legalisation of the creation of human embryos solely for research purposes.[18]

5. COUNTRIES THAT PROHIBIT HUMAN EMBRYONIC STEM CELL RESEARCH

In Italy, the law on assisted reproduction prohibits hES cell research and the Vatican has a powerful influence on Italy's policymaking. The Catholic Church has a major impact on Ireland's legislation as well. Ireland is the only European country that defends "the right to life of the unborn" in its constitution.[19] hES cell research is strictly forbidden, as is the case in Austria[20] and Norway.[21] Costa Rica, Brazil and Ecuador ban hES cell research. Only a minority of countries worldwide strictly prohibit research on hES cell cells.[22]

The question arises as to what these countries will do if life-saving therapies based on hES cell research were to be developed in less restrictive and permissive countries. There are two major options. A first one is that the government would not change its policy. Citizens would have to travel to countries or jurisdictions where life-saving hES cell therapies are allowed. This phenomenon is already known in the context of assisted reproduction and has been called 'reproductive tourism'.[23] Similarly, the strict prohibition of hES cell research could lead to 'stem cell tourism'. This option may not be very plausible since the chance is very high that the pressure of the public to have access to life-saving treatments that are available in other countries will be so great that governments will have to change their policies. This is already happening in some countries with restrictive regulatory environments. In Italy, the health minister has been put under pressure to change the strict legislation on assisted reproduction, which makes it harder for infertile people to get treatment and which endangers the life of women in order to protect embryos. More than one million Italians have signed a petition to relax the law. If the court approves the list, the government will have to accept the referendum.[24] After the scandal with Italian health minister Sirchia who had hailed a successful non-embryonic stem cell treatment of a boy with thalassaemia, but 'forgot' to mention that the treatment was based on techniques

outlawed by his policy, politicians and scientists have demanded his resignation. In Ireland, similar lobbying to relax the strict laws on embryo research has occurred. Mary Harney, whose role is similar to that of a vice president, has voted in favour of an EU framework for research on hES cells and she gets support from a great many members of the scientific community in Ireland who believe that the wider therapeutic benefit of hES cell research must be considered and who have called for a wider informed debate on the merits of hES cell research.[25] (In the case of 'abortion tourism', however, no changes thus far have occurred in Ireland).

A second policy option would be to adopt one of the compromise positions some other countries have based their policies on. The compromise that comes closest to a strict prohibition of hES cell research is based on the use-derivation distinction. Defenders of the use-derivation distinction make a moral distinction between the *use* of hES cells for research on the one hand and the *derivation* of these cells from the human embryo on the other. Using hES cells for research is considered ethically acceptable, while their derivation is not, since it involves the killing of embryos, which defenders of the use-derivation distinction consider as 'one of us'. Opting for the use-derivation distinction would be in accordance with the principle that we should always opt for the least controversial approach to reach the objectives.

Two questions arise. First, can this be done without being morally complicit with the evil deeds - the killing of embryos - committed in other countries or jurisdictions (or in the private sector)? The second question is: once one allows some hES cell research on the basis of health and research benefits - does one have compelling reasons not to allow more aspects of hES cell research for the same purposes? We will start with the first question

6. COUNTRIES THAT ADOPT THE USE-DERIVATION DISTINCTION

6.1. Human embryonic stem cell research versus embryo research

Knowing that defenders of the use-derivation distinction think the *derivation* of hES cells is immoral, we can ask on what grounds they might consider the *use* of the cellular products remaining from such acts as ethically acceptable.

A first argument -or rather a necessary assumption for those who consider embryos as 'one of us' - to justify the *use* of hES cells is that they are not equivalent to embryos, so that research with those cells, as opposed to their derivation, is not problematic because it is not considered as human embryo research.[26] The underlying idea is that hES cells are *pluripotent*, that is, they have the potential to generate any cell type in the body but not a whole organism, whereas early embryos are *totipotent*, which means they can develop into a new organism. A human embryo is generally defined as an

entity with the (inherent) capacity to develop into a human being. In a legal decision, the general counsel of the US Department of Health and Human Services (HHS) stated that: "the statutory prohibition on the use of funds appropriated to HHS for human embryo research would not apply to research utilizing human pluripotent stem cells because such cells are not a human embryo within the statutory definition." She concluded that, consequently, federal support could be given for research that uses stem cells derived from embryos by private funds. [27]

Stating that hES cell research is not equivalent to embryo research is, of course, not sufficient to justify the use-derivation distinction. One has to argue why it is ethically acceptable to use products that were obtained through an allegedly wrongful act, involving the derivation of hES cells and the killing of those who are 'one of us'. In doing so, one cannot avoid the issue of moral complicity.

6.2. Moral complicity in the stem cell derivation process

The central question in the complicity argument is whether benefiting from another's wrongdoing effectively makes one a moral accomplice to their evil deeds. With regard to moral complicity at the state level in the context of hES cell research this question runs as follows: to what extent is a government which legalises research with hES cells responsible for or complicit in the death of the embryos from which these cells are derived? According to their answer, individuals strongly opposed to embryo research might come to diverse conclusions about the acceptability of using hES cells. Whether one considers somebody as morally complicit in the killing of embryos depends on his/her view on the separation principle, which, applied to hES cell research, states that the act through which the cell products are obtained should be completely separated from the use that is made of these products.[28] If so, then those who use the cells cannot be considered to be moral accomplices in the act of derivation. This principle has been one of the central issues in debates on fetal tissue research[29] and in the use of vaccines developed from fetal material.[30] According to some people, the use of hES cells can be separated from the act of isolating the cells and the subsequent death of the embryo. But others say there is no real separation. We will consider both viewpoints.

6.2.1. Those who think the separation holds

The American Association for the Advancement of Science and Institute for Civil Society state in their stem cell report that "many individuals are convinced that not all acts benefiting from other's wrongdoing are morally impermissible, so long as one is not involved in the wrongdoing and one's own acts do not foster, encourage or lend support to it".[31] The relevant question to ask is whether the use of hES cells fosters, encourages or lends support to the killing of embryos.

Those who think the separation holds respond that those who *use* hES cells do not encourage those who *destroy* embryos unless they expressly authorise the creation or destruction of an embryo for this purpose.[32] This is why countries that allow the use of hES stem cells, but not their derivation, only approve of the use of hES cells obtained from left over embryos that were originally produced for the

purpose of satisfying a wish for a child by IVF.[33] Apart from the condition that the creation of these embryos should not be authorized by those who use the hES cells, there should also be a separation between using hES cells and authorizing the destruction of embryos for this purpose. Ronald Green argues that there need to be no causal connection between the use of hES cells and their derivation (which involves destruction) because at the present time and in the foreseeable future, embryo destruction is entirely independent of hES cell research and therapy as surplus embryos are routinely created in the practice of infertility medicine. Therefore, the argument goes, the use of hES cells is morally closer to the use of a pancreas donated from the parents of a teen murdered in gang violence than it is to anything approximating encouragement to murder.[34]

A concern exists that some parents and clinicians may justify the creation and destruction of embryos by virtue of their beneficial uses or, more generally, that this kind of research would lead to a diminishment of societal respect towards early human life.[35] However, defenders of the use-derivation distinction deny these concerns for several reasons. First, they say, there is little evidence that the use of embryos for scientific research and the benefits this brings for medicine are a motive for parents opting not to use their embryos in a parental project. In most countries the prospect of (privately funded) embryo research has always been present so doesn't have new influence on the way people decide about the destination of their spare IVF embryos.[36] Second, it is said that the demand will not be so great as to have significant quantitative effects internationally (in case the hES cells are obtained through import, as in Germany[37]) or in the private sector (in case they are obtained from the private sector, as in the US where a clear boundary is drawn between private and public research) owing these other companies' own research interest.

Some, however, are not convinced by these arguments and think the separation cannot be guaranteed because one cannot be sure that the benefits of hES cell research will induce some couples to create extra embryos for research, or to give their spare IVF embryos to researchers, rather than to include them in a parental project.[38] President Bush tried to overcome these concerns by his policy decision of 9 August 2001 allowing federal funds to be used for research on stem cells from spare IVF embryos under certain conditions (Bush's 'eligibility criteria') and - most importantly - on the condition that prior to his announcement the derivation process had already been initiated, in Bush's words "where the life and death decision has already been made".[39] Federally funded researchers in the US can only make use of the 66 stem cell lines listed in the Human Embryonic Stem Cell Registry of the National Institutes of Health (NIH). Bush explained that "this allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line, by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life".[40]

Germany considered the US's compromise position, which intended simultaneously to protect the rights of the unborn and the freedom of research, as a valid solution to solve the heated discussions preceding the policy decisions on stem cell research in Germany. The Embryo Protection Act of 1990 forbids embryo research that is not for the benefit of the embryo itself, but the Stem Cell Act of 28

June 2002 allows the import of hES cells under similar conditions as set up in Bush's decision, most important in this context, that the hES cells were derived before 1 January 2002. The underlying idea is that "the stem cells were produced abroad [...] and the 'consumption' of the embryos is already finished and irreversible before they are imported".[41]

The main argument underlying these 'compromise regulations' is that 'thanks to this policy' Americans and Germans - potential patients as well as other stakeholders - are permitted to enjoy the benefits of previous wrongful deeds, without encouraging in any way the repetition of similar deeds in the future. This viewpoint rests on the assumption that the intended goals of stem cell research can be reached by using stem cell lines from spare IVF embryos obtained in the private sector or abroad or from the existing stem cell lines that meet the standards imposed by the national law or regulations. They predict that the exclusion of new cell lines from spare embryos or stem cell lines derived from embryos solely created for the purpose of the research will not have significant negative impact on the progress of research.[42]

6.2.2. Those who think the separation does not hold

Several arguments have been advanced to show that the separation between the use and derivation of hES cells cannot be guaranteed, and thus that research on cell lines already established by destroying human embryos does not avoid moral complicity in the killing of those who some consider as 'one of us'. One of the most important objections to the policy decisions of the US and Germany is that a policy limitation to 'already existing cell lines' is an arbitrary line which may not hold in practice.[43] If hES cells do show clinical promise, and American and German researchers fall behind because of restrictions on their access to the cell lines that meet the required criteria, political leaders will come under pressure from researchers, (potential) patients and other stakeholders in hES cell research to change the regulations. The argument is that once one accepts that a restrictive amount of cell lines can be used for research, because of the great health benefit of the citizens, it is hardly possible not to extend the list of available stem cell lines when the existing ones appear to be an insufficient source, particularly where spare embryos are continually created as part of assisted reproduction.[44] In 2003, eleven US house republicans expressed their concerns about the quality, longevity, availability and terms of use of the stem cell lines in the NIH's hES cell registry and asked the President to review the 2001 policy for allowing for the creation of new hES cell lines.[45] Ruth Faden and John Gearhart (who was the first to derive and culture embryonic germ cells in 1998) have stated that the hES cell lines approved by President Bush are inadequate to advance stem cell science. There are too few of them to accommodate the genetic diversity in our population and all were prepared using mouse cells, which may rule them out for clinical trials because of the risk that an animal virus might be passed to patients. Moreover, it is not possible to use federal funding to generate or study stem cells derived from embryos with genetic defects or diseased genes. Such stem cell lines would be invaluable in gaining knowledge about the molecular basis of disease and in seeking ways to prevent or treat them.[46] Two recent studies shed light on other restrictions of the approved cell lines. The first, led by Fred Gage of the Salk Institute in La Jolla, California, and Ajit Varki of the University of California in San Diego, shows that the

approved hES cell lines share a previously unrecognised trait that fosters rejection by the immune systems, diminishing their potential as medical treatments. A second study, led by Carol Ware of the University of Washington, is comparing characteristics of the 14 of the 22 Bush-approved cell lines. At least 5 will never be useful in a clinical context because they are so difficult to grow; moreover, each colony has a tendency to turn into a particular body cell, suggesting more than the 22 colonies will be needed if the field is to reach its full potential.[47]

Given the restricted usefulness of the approved cell lines, the question arises whether the US and Germany will allow for research on other cell lines that do have the right characteristics to reach the intended research goals, which would be in accordance with the subsidiarity principle. But what if these lines also appear insufficient; will they allow more hES cell research if this is deemed necessary to reach the research goals? Once one allows some hES cell research on the basis of health and research benefits - it may become very difficult to find compelling reasons not to allow more aspects of hES cell research for the same purposes.

Another problem with separation is that those who use hES cells lend support and encourage those who derive the cells if they pay for these cells. In the US government funding is foreseen for research that uses hES cells, but not for researchers who derive hES cells. According to Alex Capron, Director of Ethics, Trade, Human Rights and Health Law at the World Health Organization, the distinction between paying for the use of stem cells and paying for their derivation is merely 'bookkeeping fiction'. The funding provided for studies using hES cells would flow directly to researchers deriving those cells, perhaps even in an adjacent lab. The only true difference would be that the federal funds would not go directly as a salary and laboratory expenses for the derivation process but indirectly as funds to obtain hES cells.[48]

The most important argument against the separation, however, is that research which involves the use of hES cells and research which involves hES cell derivation are inextricably linked. Both types of research are part of one single scientific project. Apart from complicity through causal responsibility for an action, the intention to collaborate in order to reach the same goal can also cause complicity.[49] Those who derive hES cells will use the hES cells and/or donate them to other researchers who will use them in research. Those who use hES cells know that those who derive hES cells had this intention. Both share the intention that hES cells are used in order to reach the intended research aims of stem cell research and they both know that using them necessarily requires their derivation, thus the killing of embryos. The shared intentions of those who use and those who derive hES cells, makes the first ones complicit in the derivation process. Apart from this, there is also a symbolic association. Benefiting from evil may imply that one implicitly approves of the wrongful act or, at least, finds it not so repugnant as to renounce the benefits deriving from this evil. We will come back to this issue later. We can conclude that there no real separation between the use of hES cells and their derivation. Given the lack of separation, support for research using hES cells is surely acceptable only to the extent that the process is acceptable. The use-derivation distinction cannot be sustained.

7. NO USE-DERIVATION DISTINCTION, BUT DO WE NEED ONE?

We have concluded that the use-derivation distinction cannot be guaranteed in practice. The question that arises is whether we really need such a distinction. To answer this question we need to investigate whether the people for whom the use-derivation compromise is intended - that is, those who consider the embryo as one of us - really need such a compromise and how this compromise relates to already widely accepted practices in societies that base their stem cell policy on the use-derivation distinction. Let us start with the last question.

7.1. Consistency between our beliefs, practices and regulations

In most countries with a stem cell policy based on the use-derivation distinction, abortion is widely practiced. In the US, more than one in five pregnancies ends in an abortion. In Germany, abortion is technically illegal, but women are not penalized, provided they receive counselling at a state-approved center, which may then issue them a certificate. Moreover it is astonishing that governments that want to protect the embryo and its human dignity, such as Germany, make the abortion pill RU-486 available. [50] Since September 2000, when the US Food and Drugs Administration approved RU-486, more than 460,000 American women have chosen this option.[51] Even more incompatible with strict views on embryo protection is that 10,000 children are born each year using IVF techniques and no stigma is attached to children so born, even though the IVF techniques were developed through research on embryos. This is because the respect most people now have for the early *in vitro* embryo is already low. Many people concern for some kind of protection for embryos, but these feelings can change and often depend on whether or not an embryo is involved in a parental project. IVF is a broadly accepted practice and has become routine in most countries. It is a practice in which thousands of spare embryos are intentionally created that will be discarded or will be used in medical experiments. In the US alone, more than 400,000 embryos are stored in freezers awaiting their destination, which in most cases will be 'the bin' or scientific research. Once people accept the creation and sacrifice of embryos to benefit infertile people, it seems inconsistent to condemn the creation and sacrifice of embryos to benefit those whose lives might be saved by stem cell therapies.[52] Moreover, it is important to point out that IVF, cryopreservation, Intracytoplasmic Sperm Injection (ICSI) and other techniques were all developed through research on embryos that came into being only for the purposes of the experiment. Some governments consider this type of experiment to be unacceptable from an ethical standpoint, although the results of such experiments are applied without any qualms and in most countries have even become routine. The same is true for embryo experiments that are currently done to develop methods to improve, facilitate or make reproduction possible, such as the development of better methods of *in vitro* culture and IVF, and of gamete and embryo storage.[53]

Many embryos are created and sacrificed for no good purpose, because, for example, the mother did not think about the possibility of pregnancy and then decided that pregnancy and childbirth were too

awful a prospect to contemplate. Equally, many embryos are created and sacrificed for a good purpose - as part of procreative endeavour that is completed or abandoned. These 'spare' embryos are then often destroyed, the good purpose for which they were created having been accomplished. Given that many thousands indeed many hundreds of thousands of embryos have been and will continue to be created to help to establish future lives, should others (or indeed these embryos themselves) not be created to help save present and future lives? Why then might it be wrong deliberately to create an embryo for the good using its tissues and cells might do? Grant the legitimacy of creating embryos that will perish as part of assisted reproduction, something that inevitably happens in all assisted reproduction techniques (ART) and in all countries that permit ART, then consistency demands permitting embryo sacrifice for morally equivalent purposes.[54] Even in Italy where current law requires the implantation of all embryos created in ART[55] it is recognised that such a law is effectively unenforceable because of the 'impossibility' for forcibly inserting embryos into unwilling and resisting women. Moreover, as we shall shortly see, these problems of consistency apply as much to 'normal' reproduction as they do to assisted reproduction.

7.2. There is evil and then there is 'evil'

It seems likely that if therapies were to be proved for serious illnesses using embryo derived stem cells, the people of Germany and the US - countries which have condemned such research - would want to use them and their governments would find it difficult, if not impossible, to say 'no'. Even if the governments did refuse to accept effective drugs developed from hES cells, the Treaty of Rome, guaranteeing free movement in the European Union, would permit free movement of citizens for 'stem cell tourism' to access therapies from neighbouring states. Equally, it would be unlikely (although logically consistent) for such governments to criminalise attempts to access such therapies as they perhaps do (or would be justified in doing) for those of their citizens who attempted to access, say, child sex in Asia contrary to the Laws in their home European state. How would we feel about the citizens of countries which have declared research on embryos unethical and have outlawed such research? Would they be hypocrites or monsters, or both? Should they so regard themselves? We think we would and should feel differently about a country which, while officially believing and saying that using embryo-derived stem cells is evil and hence that to use benefits derived from such cells would be benefiting from evil nonetheless accepted such benefits from other sorts of benefiting from evil.

Does this mean that we feel that there are evils and evils - different levels of evil or does it show that we do not actually believe that certain things claimed to be evil are in fact evil properly so called?

There are many possible, but two plausible, explanations for intuitive reactions here. The first is that there are indeed degrees of evil. Many believe adamantly that we should not accept any conceivable benefits flowing from the Nazi atrocities before and during the Second World War. For example the notorious 'Dachau Hypothermia Study' in which concentration camp inmates were subjected to lingering death in freezing water allegedly to study the survival possibilities for German pilots who

crashed into the freezing North Sea or Atlantic Ocean. This 'science' has been condemned on many grounds, not least for the fact that it was poor science as well as unspeakable cruelty. However, opinions have differed about the ethics of using any real knowledge gained from such bestiality.[56] Those who think that the embryo is really 'one of us' and that experimenting on 'innocent' embryos would be, is in fact, like experimenting on innocent concentration camp inmates, should however surely think there is a strong link between the two activities. There are two ways of resolving this. Either one could claim that there is in fact nothing wrong with benefiting from evil provided that the benefit is not responsible for the commission of the evil or for the commission of future analogous evils. That might be very difficult to establish in fact, although the principles can be articulated clearly. While there may be much to be said for this approach it is unlikely to satisfy those who find the Nazi atrocities so repugnant that the prospect of any good coming from them is simply unacceptable. The alternative is to suggest that although people have said that embryo research is an evil, even those who condemn it and accept the embryo as 'one of us' do not in fact really believe any such thing.

7.3. Does anyone really believe that embryos are moral persons?[57]

Stem cell research and therapy using human embryos, and indeed all other therapeutic or research uses of embryos, might be successfully defended by drawing a distinction between what people say and what they do, or rather to point out that there may be an inconsistency between the beliefs and values of people as expressed in their statements on the one hand and by the way they behave on the other. 'To know the good is to do the good and to know the bad is to avoid the bad' and while this ancient 'truth' of course has to allow for weakness of will it does tell us something about consistency and sincerity. Although many people including most so called 'pro-life' or 'right-to-life' supporters are prone to make encouraging noises about the moral importance of embryos, and even sometimes talk as if embryos have, and must be accorded, the same moral status as you and me; they very seldom, if ever, behave as if they remotely believed any such thing. Taking for the moment as unproblematic the idea, made famous by Socrates, that 'to know the good is to do the good'; many pro-life advocates or others who believe that the embryo is in a real sense 'one of us' do not behave consistently with their professed beliefs about what is good.

One would expect that those who give full moral status to the embryo, who regard it as a person like us, would both protect embryos with the same energy and conviction as they would do with their fellow adults and would mourn their loss with equal solemnity and concern. This however they do not do. It is true that some extreme defenders of the embryo in the US have taken to murdering obstetricians who perform abortions, but those same individuals are almost always inconsistent in some or all of the following ways.[58]

We know that for every live birth up to five embryos die in early miscarriages.[59] Although this fact is widely known and represents massive carnage, pro-life groups have not been active in campaigning for medical research to stem the tide of this terrible slaughter. Equally we know that for the same

reasons the menstrual flow of sexually active women will often contain embryos. Funeral rights are not usually routinely performed over sanitary towels although they often contain embryos. In the case of spare embryos created by ART there has not been the creation of a group of pro-life women, offering their uterus's as homes for these surplus embryos. Indeed anyone engaging in unprotected intercourse runs substantial risk of creating an embryo that must die, and yet few people think that this fact affords them a reason either to refrain from unprotected intercourse (it is more usually the fear of creating an embryo that will not die that motivates them) or to press for medical research to prevent this tragic waste of human life.[60]

It is notorious that many would-be protectors of the embryo are prepared to permit abortions in exceptional circumstances, for example, to save the life of the mother or in the case of rape. However, in the former case the right course of action for those who believe the embryo has full moral status is to give an equal chance to the embryo or the mother (perhaps by tossing a coin) in cases where one may survive but not both. In the case of rape, since the embryo is innocent of the crime and has therefore done nothing to compromise its moral status, the permitting of abortion by those who give full status to the embryo is simply incoherent.[61]

These phenomena provide reasons for thinking that even if the views of those who believe the embryo to have the same moral status as normal adult human beings cannot be conclusively shown to be fallacious, at least they can be shown to be inconsistent with the practice of most of those who profess such views, and that the 'theory' is not therefore really believed by those who profess, or if believed is actually compatible with the lives that human beings must, of necessity, lead. hES cell research is then ethical and because of its immense promise also obligatory.

8. CONCLUSION

The use-derivation distinction is not a solid ethical basis for stem cell policy. The reasons are twofold. First, the separation between using and deriving hES cells cannot be guaranteed in practice. Consequently, support for using hES cells is acceptable only if the stem cell derivation process is acceptable. Secondly, those who claim the embryo should be protected as if it was a person are committed to a position even they do not uphold in their practices. Given that they are willing to treat the embryo as a mere means in other practices, the use-derivation distinction becomes a redundant compromise. Grant the legitimacy of creating embryos that will perish as part of assisted reproduction and other practices, then consistency demands permitting embryo sacrifice for morally equivalent purposes in all countries that permit these practices.

ACKNOWLEDGMENTS

I wrote this paper together with John Harris, Sir David Alliance Professor of Bioethics, School of Law, University of Manchester.

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16 Belgian Senate. *Belgian Law Concerning Research on the Embryo In Vitro*. 2003 May 11. Human Fertilisation and Embryology Authority. HFEA Act 1990 extended by the Human Fertilisation

and Embryology Regulation of 2001. In November 2004, the Swedish government Bill 2003/04:148 on stem cell research was enacted. The Bill explicitly allows the creation of embryos through somatic cell nuclear transfer and will come into force on the 1st of January 2005. The Dutch Embryo Act of 2002 prohibits the creation of human embryos for research. However, this ban is not irreversible and could be lifted by Royal Decree within five years after the Act came into effect.

17 These terms are used in Green R.M. *The Human Embryo Research Debates: Bioethics in the Vortex of Controversy*. Oxford, New York: Oxford University Press; 2001.

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abortion and the use of fetal material for research and therapies. Many countries have tried to guarantee this separation by imposing conditions on the performance of abortions and on the donation of fetal tissue in laws and regulations. Shorr A.F. Abortion and fetal tissue research - some ethical concerns. *Fetal Diagn Ther* 1994; 9(3):196-203. Rankin J.C. The fetal tissue debate on complicity. *Hastings Cent Rep* 1990; 20(2):50.

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57 In this section we have benefited from discussions with Dan Wikler.

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61 Janet Radcliffe Richards made this point well in her book *The Sceptical Feminist,* Penguin Books, Harmondsworth 1982.

PAPER 2
THE DISCARDED-CREATED DISTINCTION

Adapted from:
Devolder, K. Human embryonic stem cell research: why the discarded-created distinction cannot be based on the potentiality argument. *Bioethics* 2005; 19(2):167-86.

Devolder, K. Creating and sacrificing embryos for stem cells. *J Med Ethics* 2005 Jun; 31(6):366-70.

1. ABSTRACT

The compromise position that accepts the use and derivation of stem cells from spare in vitro fertilisation (IVF) embryos but opposes the creation of embryos for these purposes is a very weak ethical position. This paper argues that whatever the basis is on which defenders of this viewpoint accord intrinsic value to the embryo, once they accept the creation and sacrifice of embryos to benefit infertile people with a child-wish, they do not have a sound moral argument to condemn the creation and sacrifice of embryos to benefit ill and injured people.

2. THE DISCARDED-CREATED DISTINCTION

One of the central questions in the current stem cell debate is whether human embryonic stem (hES) cell research should be allowed, and, if so, under what constraints. Discussions about the regulation of hES cell research are a stumbling block in developing stem cell policy. On the one hand there is a growing consensus that of all types of stem cell, hES cells hold most promise for particular and important therapeutic and research aims.[1] On the other hand, there is the controversial issue of 'killing' human embryos through stem cell derivation.

Most of the participants in the stem cell debate, and especially those who are involved in policy making, opt for one of the possible compromise positions. They do not want to block hES cell research, but attempt to articulate at least some grounds for restraint in the use and derivation of hES cells in order to protect the embryo. I will focus on the compromise position that accepts the use and derivation of stem cells from spare in vitro fertilisation (IVF) embryos, but not of stem cells obtained from embryos created solely for the purpose of stem cell derivation, so-called 'research embryos'. Many European advisory and regulatory bodies defend this position[2] and a survey of public attitudes in nine European Union countries has shown that the majority of the participants in this research project also share this viewpoint.[3]

I will argue that the ethical position that makes a moral distinction between the use of spare embryos and research embryos -the so-called discarded created distinction[4] (DCD)-is a very weak position. The main reason is the inconsistency between the 'revealed' beliefs (that is, beliefs revealed by one's acts or omissions) of its defenders and their professed beliefs. I will argue that whatever the basis is on which defenders of this viewpoint accord intrinsic value to the embryo, once they accept the creation and sacrifice of embryos to benefit infertile people with a child-wish, they do not have a sound reason to condemn the creation and sacrifice of embryos to benefit ill and injured people. Furthermore, I will show that an approach to hES cell research which would also allow the creation of embryos solely for the derivation of stem cells would be more compatible with the revealed beliefs of those who currently defend DCD, and with widely shared values, in particular the alleviation of individual human suffering.

3. ARGUMENTS IN FAVOUR OF DERIVING STEM CELLS FROM SPARE IVF EMBRYOS

Defenders of DCD find the use and derivation of stem cells from spare IVF embryos ethically acceptable but not the creation of embryos solely for these purposes. The latter could be created by IVF but could also be the result of somatic cell nuclear transfer (SCNT)[5] or embryo splitting. Let us examine the arguments underlying this position.

First we have to ask ourselves why the defenders of DCD want some hES cell research to go forward. Why do they accept the use and derivation of stem cells from spare IVF embryos?

Their motivation is grounded on one or a combination of the following widely accepted principles. Among these are the principle of freedom of research[6] and the principle of progress,[7] which state that restraints on scientific research are inherently offensive and generally unjustifiable[8] and that we have a right to acquire new knowledge. The principles of beneficence and non-maleficence[9] state that it is right to benefit people if we can, and wrong to harm them. hES cell research could provide knowledge and therapies that would benefit thousands of people. Another principle referred to by defenders of DCD is the principle of proportionality,[10] which states that the research has to serve an important purpose, such as a major health interest. In its recommendations on stem cell research, the US National Bioethics Advisory Commission (NBAC) expressed it this way: "In our view, the potential benefits of the research outweigh the harms of the embryos that are destroyed in the research process".[11] Another principle used to defend DCD is the principle of subsidiarity,[12] which states that we have to choose the less contentious means of achieving the intended goal. Defenders of DCD apparently consider spare embryos as a necessary and also a sufficient stem cell source to reach the intended research goals. However, as John Harris has pointed out,[13] the most important principle in defence of the use of spare embryos for research is the principle of waste avoidance, which states that, other things being equal, it must be better to make good use of something than to allow it to be wasted. With regard to hES cell research the argument goes that spare IVF embryos are going to be destroyed anyway because they are no longer needed in a procreation project, and that it is better to use them for a greater good-that is, for research and therapies, than to allow them to be wasted. After all, it does not alter their final disposition.

Many people would agree that these are all valuable principles.[14] Of course it is better to benefit people than not to benefit people or to cause them harm, and of course the research has to serve important purposes and valuable things should not be wasted. None of these principles, however, suffices to justify DCD. They express why one wants some hES cell research to go forward, and why one supports the use and derivation of stem cells from spare embryos, but it does not follow from these principles why one opposes the creation of research embryos. It is, for example, perfectly possible to argue against the waste of spare embryos while at the same time considering the creation of research embryos as ethically acceptable.

The relevant question here is what exactly makes it unethical to create embryos solely for research. Why is the use and derivation of hES cells from research embryos 'ethically worse' than from spare embryos, and this to a degree that justifies the prohibition of the creation of research embryos?

4. ARGUMENTS AGAINST THE CREATION OF RESEARCH EMBRYOS

4.1. Instrumentalisation of the embryo

The principal objection of advocates of DCD to the creation of research embryos is that through this act the embryo is not treated with the appropriate respect such a form of human life is entitled to, because it is used merely as a means to an end. The underlying idea is that respect for human beings prevents the instrumental use of embryos,[15] an act that, according to some, violates 'human dignity'.[16]

Most advocates of DCD genuinely think the embryo deserves 'special' respect. They consider it to be more valuable than any other human cell or tissue. However, by accepting the creation of spare embryos and their use for research, they apparently believe that its right to life can be weighed up against other values and interests and that human dignity is not violated per se by using early embryos as a means for research.

This raises the following question: if defenders of DCD do not consider the embryo as a person and accept the creation and sacrifice of embryos to help infertile people and their use for research, should they not also accept the creation and sacrifice of embryos to help to cure ill and injured people? After all, in both cases embryos are created as a means to alleviate human suffering and increase human wellbeing. Apparently, the argument of instrumentalisation alone does not suffice to justify DCD. It is not a logical consequence that one opposes the creation of research embryos. One can agree that the embryo is instrumentalised in an IVF treatment or in embryo research without disapproving of this.

Defenders of DCD reply to this that what makes the difference, in other words, what justifies DCD is that creating research embryos involves a "distinct kind of exploitative attitude, reflecting the thought that an embryo is something whose entire significance may be characterized by the external purposes for which we brought it into existence-the clearest possible case of treating something as a 'mere means'".[17] A similar argument was expressed by the NBAC in their 1999 report on stem cell research: "the act of creating an embryo for reproduction is respectful in a way that is commensurate with the moral status of embryos, while the act of creating an embryo for research is not".[18]

But what is meant by "respectful in a way that is commensurate with the moral status of an embryo"? And why does the creation of research embryos involve a "distinctive kind of exploitative attitude"? Let us investigate these arguments and see whether they can justify DCD.

4.2. The creation of research embryos is not commensurate with the moral status of the embryo

Here we first have to ask ourselves which moral status defenders of DCD accord to the human embryo. The fact that they accept 'destructive' embryo research shows that they do not consider the embryo as a person and even do not accord a moral status to it close to that of a person. Nevertheless, they believe it has intrinsic value-value independent of people's intentions-and, therefore, merits 'special respect'.

4.2.1. Human dignity and symbolic value of the embryo

Some say the embryo has intrinsic value because it possesses *human dignity*.[19] We should note here that there is no agreement on the meaning of human dignity. It is a vague expression that has to be clarified when used as an argument. Moreover, defenders of DCD apparently think that the fact that embryos possess human dignity does not imply that we have to protect them under all circumstances. After all, they accept the creation and sacrifice of spare IVF embryos. Consequently, the mere reference to human dignity cannot justify DCD.

Some say the embryo has to be protected because it has *symbolic value*. [20] In symbolic issues like this, however, it is not really the embryo that is at issue, but the impact of certain practices on our respect for human life. The relevant question here is whether the creation of research embryos will weaken our communal respect for human life in some way that IVF or the experimental use of spare embryos does not. There is nothing to suggest that this will be the case.[21] Consequently, referring to symbolic value is not a sufficient argument to justify DCD. But taking into consideration the question of what the embryo is a symbol of brings us to a viewpoint on the embryo that most, if not all, defenders of DCD (implicitly) share. Therefore, this viewpoint is also more conducive to finding another valuable approach to hES cell research that is more compatible with the revealed beliefs of defenders of DCD. This widely shared viewpoint forms the basis of the Dutch Embryo Act[22] and is expressed by the Health Council of the Netherlands as follows: "since it is human in origin and has the potential to develop into a human individual, the embryo has intrinsic value on the basis of which it deserves respect".[23] The French National Consultative Ethics Committee defends the position that "the embryo or foetus has the status of a potential human being who must command universal respect".[24] Both advisory bodies defend DCD and both believe the embryo has intrinsic value because it is a *potential human being*, a potential person.

4.2.2. The embryo as a potential person

The expression 'the embryo is a potential human being' or a 'potential person' seems to express something which is intuitively certain and acceptable and which opens the way to ethical consensus. However, the expression is vague. This is evidenced by its use to defend opposing views on embryo research. Some hold that the embryo, because it is a potential person, deserves our full moral respect and protection. The concept of 'potential person' is then used as a step in the argumentation for the prohibition of 'destructive' embryo research. Others say that because the embryo is only a *potential* person it does not merit full respect, and have used the potentiality argument *in defense* of human embryo research.[25]

If one uses the expression 'the embryo is a potential person', one has to explain what is meant by it and why it can serve as an argument to defend a certain moral position. One cannot singularly appeal to the fact that an embryo could become a person to give it the protection we normally give to persons. Since the development of SCNT, every somatic cell of the human body is, in this sense, a potential person. A necessary condition for the realization of this potential is the application of the nuclear

transfer technique.[26] Here we have come to a very important and useful aspect of the concept of potentiality: its conditions.

The only thing on which everyone agrees concerning the meaning of 'potentiality' is that something that is potential is not actual but can become actual *under certain conditions*. These conditions can depend on *internal* and *external* factors. With regard to the 'embryo as a potential person', the internal factors are the characteristics of the embryo itself (e.g. its genetic constitution, its developmental potential). The external factors could be both in the genesis of the embryo (e.g. the application of SCNT) as well as beyond (e.g. being chosen to be implanted in the womb, becoming a spare embryo, being aborted). The external conditions, related to intentions of people, can depend on internal conditions (we select a particular embryo because it has characteristics give it a higher chance for successful implantation), but do not necessarily do so (they can depend on other intentions, e.g. a woman who does not want a child). Those who radically oppose hES cell research only take into account the internal conditions of potentiality and are of the opinion that the moral status of the embryo can only be deduced from the characteristics of the embryo itself, that is, from its ontological structure.[27] They see potentiality as purely interior. What matters is that 'in the normal course of events' the embryo develops into a person. Whether or not it will actually become one makes no difference for the protection we have to give it.

Defenders of DCD also grant a moral status to the embryo on the basis of its internal characteristics - they consider the embryo to be more valuable than any other human tissue or cell - but *in fact* they also take into account the *external* factors of potentiality, based on people's intentions. If they do so, they cannot justify DCD on the basis of the potentiality argument. Let me explain.

4.2.2.1. Internal conditions for potentiality

With regard to the genesis of the embryo and the internal conditions that have to be fulfilled to become a person, we may ask ourselves what is meant by 'potentiality'. If defenders of DCD keep on stressing that the embryo has *intrinsic* value, what exactly do they mean?

They generally mean that all human embryos have something in common, namely the biological and genetic constitution to develop into a human being. This is often reflected in the definition of an embryo; for instance, the Belgian Senate's Bill on Embryo Protection defines an embryo as a "cell or cohesive system of cells with the capacity to develop into a human being".[28] Because of this potential, the argument goes, the embryo deserves special respect. There exist various interpretations of the concept of potentiality.[29] Some see it as an 'all-or-nothing' matter. Potentiality is then interpreted as the capacity to 'become' or to 'produce'[30] something, in virtue of the operation or expression of its inherent, physical properties, and given circumstances that make the operation or expression of these properties possible.[31] Whether or not the embryo actually becomes a person, is not relevant to the protection we have to give it. The potential of the embryo cannot 'unfold' or diminish,[32] it can only

be frustrated.[33] A similar view is what we might call the *possibility* view in which the potentiality of an embryo to become a person is seen as the *possibility* that its development into a person will, or would under favourable conditions, occur in the future.[34] Reasons for protection are not the present potentialities, but future outcomes.[35] Killing an embryo is not a violation of some right of the embryo, but of the person into which it may develop. Others see potentiality as a matter of degree. They acknowledge a link between potential and (inherent) probability.[36] The more probable it is that an embryo will become a person, the more protection it should get. We can distinguish certain factors playing a part in the probability that an embryo develops into a person: (1) the extent of resemblance to the human bodily form, (2) the extent of independence or autonomy with respect to a particular environment (e.g. the womb), and (3) the fact that the embryo has passed some critical and easily identifiable marker event(s) in its development (individuation, development of the spinal cord, brain activation, becoming a sentient being, etc.).

According to those who defend the gradual approach of potentiality[37] the value of an embryo increases gradually during the course of its development. Some have a single criterion approach, which means that they choose one of the aforementioned factors in according a moral status to the embryo. For example, one may be of the opinion that the embryo's potential depends on (1) and that therefore a nine-week-old fetus has more value than a 4-week-old fetus, which then has more value than a six-day-old embryo. Others defend a multi-criteria approach.[38] They are of the opinion that a variety of criteria interact and work together to lead to a mounting sense of concern and ultimately to judgments of worthiness-of-protection. According to them, in determining the status of an embryo or a fetus we have to look at all these qualities and their interrelationships. The greater the number of criteria an embryo or fetus meets, the closer it comes to meriting full protection. This view has the advantage that it expresses what many people feel intuitively when one says that an eight-month-old fetus is more human than a one-week-old embryo. After all, although there is a continuous, gradual development from the zygote to a foetus several months old and to the newborn baby and beyond, we can hardly deny that major changes occur in the course of this development.[39]

However, I do not intend to analyse the various views on the intrinsic value of the embryo in this paper. My point is that it is hard to justify a difference in moral status between both spare and research embryos on the basis of any of the aforementioned criteria of potentiality. Both have the 'intrinsic' (or 'inherent') capacity to develop into a person, and in both cases this capacity will be frustrated when they are used for research. Furthermore, spare and research embryos have clearly as much or as little 'intrinsic' chance of becoming a human person. As much, because they both have the intrinsic possibility of developing into a person under favourable conditions (in both cases, however, this possibility is removed by human intervention[40]), and as little in the sense that both are *in vitro* embryos which cannot develop into a person without human intervention.[41] With regard to the gradual view of potentiality, it suffices to say that both spare and research embryos score equally low on each of the aforementioned criteria related to probability.

Consequently, with regard to their *intrinsic* or *internal* potential, there is no moral difference between spare and research embryos. Both have (or have not) the intrinsic capacity to develop into a person because of their genetic constitution and other characteristics of the embryo itself, and in both cases this capacity, this potentiality, will be frustrated when they are used for research.
So what can it mean if one says that the creation of spare embryos is more commensurate with the moral status of embryos?

4.2.2.2. External conditions for potentiality: the parental project

The following consideration may establish a large consensus among those who consider the creation and 'killing' or 'sacrifice' of spare embryos ethically acceptable. Whatever the human emotions and opinions in relation to the embryo or the fetus may be, as soon as it becomes a question of the procreation project, the embryo is experienced as 'the expected child' from the moment a woman knows she is pregnant or, in case of IVF, the embryo is created *in vitro*.[42]
The value people who undergo an IVF treatment ascribe to in vitro embryos is typically variable and rises considerably as soon as embryos are actually used in a parental project and decreases when they are no longer used in such a project. They are then referred to as 'spare', 'surplus or 'supernumerary'. One of three options for the conceivers or the "owners" of spare embryos is to donate those of good quality to another couple (in which case they will not be considered as 'spare' anymore, because they are again included in a procreation project), but most of them will be donated for research or will be discarded.[43] Many people even forget that a number of their embryos are still frozen or do not even answer fertility clinics when asked what should be done with their surplus embryos.[44] And in some countries with restrictive regulations, such as Germany and Austria, spare embryos can be cryopreserved for no more than one year. If, by then, they are not used for reproductive purposes by their conceivers, they must be destroyed.
Apparently, people who undergo IVF treatment and those who accept these practices believe that not every embryo's intrinsic or inherent potential to become a person must be realised. The embryo as such is not the object of great value and almost absolute protection, but the embryo that is intended to lead to the birth of a desired child. Not only couples or individuals who create spare embryos, but also those who approve of this, apparently believe that the enhanced chance of a successful pregnancy and of fulfilling their wish for a child outweighs the moral value of each of the embryos. After all, they know beforehand that most of the created embryos will die, including some of 'top quality'.

4.3. Intention/foresight distinction

Defenders of DCD often justify the sacrifice of spare embryos by referring to the doctrine of double effect or to the 'intention/foresight distinction'.[45] They say that embryos in a fertility treatment are created for the purpose of procreation and that the existence of spare embryos and their 'destruction' is merely a non-intended side effect. The doctrine of double effect is invoked to permit acts which will foreseeable kill innocent people, on the condition that these deaths are foreseen but not intended and where they are not out of proportion to the good aimed at.[46] First of all, we have to ask ourselves

what the alternatives are to omitting to reach the good of which the creation of spare embryos is a side effect. The alternative is that we would not help infertile people by IVF. Apparently, those who accept IVF are convinced that helping infertile people outweighs the foreseen death of hundreds of thousands spare embryos. Secondly, there is the question of proportion. Can we speak of a 'side-effect' when we know that for every IVF embryo that grows to term, around 25 embryos must die?[47] Moreover, it is not about saving millions of human lives by the unintended but foreseeable death of hundreds of thousands spare embryos, as could be the case in stem cell research; it is about helping people to fulfil their wish for a child. We will come back in more detail to both points later. Thirdly, if we apply the principle of double effect to the issue of spare embryos, the non-intended side effect is 'generating spare embryos' and not 'research on spare embryos' or 'discarding spare embryos'. Experimenting is merely a new action, which must be justified on another basis.[48]

The basis on which defenders of DCD justify research on spare embryos is a consequentialist argument, namely that the respect we have with regard to the human embryo as a potential person has to be balanced against other values and needs, namely the development of therapies.

But is the deliberate "destruction" for research of thousands of spare embryos-with the same intrinsic status as any other embryo-commensurate with their moral status as a potential person?

Yes, if this moral status is seen as variable and dependent on people's intentions-for example, whether or not to include it in a parental project. Defenders of DCD apparently think that the potential of each created embryo to become a person should not be realised per se. Their protection can be weighed up against other values, such as the autonomy of the conceivers of the embryos who have to give their informed consent about the destination of their spare embryos (after all, an other option could be that each spare embryo should be adopted out).

Why cannot we then create embryos for stem cell research? After all, their intrinsic potential is also weighed up against other values and needs, namely the important research purposes.

4.4. Spare IVF embryos have a chance to become a person

Defenders of DCD defend their viewpoint by stating that the creation of embryos for stem cell research entails a 'different kind of exploitation' because unlike a research embryo, a spare embryo has had a chance of becoming a person and we have therefore treated it with more respect than a research embryo.[49] In their opinion, an embryo created for research is clearly being used merely as a means to an end, because it has no prospect of implantation, whereas at the time of creation the spare embryo had a prospect of implantation, even if, once not selected for implantation, it would have to be destroyed.[50]

Is this reasoning strong enough to justify DCD? Consider the following thought experiment: suppose we generate research embryos, because it is the best way to reach the promising research goals. For the sake of argument, we might propose making a random selection of the same percentage of spare embryos that become a human from the research embryos and donate them to infertile couples who need a donor embryo. The percentage of research embryos that becomes a human would then be the same as that of the spare embryos that do so. Consequently, they would have had the same chance of becoming a person.[51]

If we would put this into practice, what results would we get? We know that about 3.5%[52] of the created embryos in an IVF treatment become a person. To be more correct we would need to donate more than 3.5% of the research embryos to infertile couples, since only a fraction implants and goes to term. Suppose we would donate 10% of the research embryos. In the UK, the creation of research embryos has been allowed since 1990. Human Fertilisation and Embryology Authority (HFEA) figures show that between 1991 and 2000, a total of 925 747 embryos were created by IVF, of which only 118 were solely for research.[53] Would defenders of DCD, bearing in their minds that in the same period 53 497 spare embryos were donated for research and 294 584 were destroyed, feel more comfortable if they knew we had donated 12 (10% of 118) of these research embryos to infertile couples for adoption? What argument would supporters of DCD put forward against this proposal?

I think they would not have a strong argument. I think they even would not have a sound argument if we proposed to create research embryos and guarantee that one of them will become a person. After all, every embryo has had a chance of becoming a person and thus was treated as an end in itself. Without this proposal, none of them would have had a chance of existing at all. The survival chance of each embryo was not optimised because of other important values (helping ill and injured people). But this is also the case in IVF treatments, which put high risks on the embryos and decrease the intrinsic chances on survival of the embryos. (To protect women against multiple ovarian stimulation, embryo sparing techniques are rarely used, and the freezing procedure puts high risk on embryos of good quality-50% of good quality embryos do not survive this procedure.)

The idea of taking a certain percentage out of research embryos might sound a bit absurd, but it helps to show that, apparently, defenders of DCD think that it is not that important to realise the intrinsic potential of each deliberately created embryo. It seems inconsistent that defenders of DCD are offended by the idea of the creation of research embryos as to oppose it despite the enormous benefits of the research for millions of people, while at the same time doing so little to optimise the intrinsic potential of embryos and instrumentalise them in IVF and research practices.

Moreover, the fact that defenders of DCD so strongly reject the making of research embryos is rather astonishing. As we all know, the IVF technique, the method of cryopreservation, intracytoplasmic sperm injection (ICSI), and other techniques were all developed through research on embryos that only came into being for the purposes of the experiment. So defenders of DCD consider this type of experiment to be unacceptable from an ethical standpoint, although the results of such experiments are applied without any qualms and in most countries have even become routine. The same is true for embryo experiments that are currently done to develop methods to improve, facilitate, or make reproduction possible, such as the development of better methods of in vitro culture and IVF, and of gamete and embryo storage.[54]

4.5. Embryos can only be instrumentalised for reproduction

One possible reply of defenders of DCD is that in the case of embryo experimentation for the improvement of, for example, culture conditions or other IVF procedures, embryos are instrumentalised for reproductive purposes, and this is justified because it is the embryo's 'function'

to be used for reproduction.[55] I think this argument is very weak, primarily because it does not take into account what is in the interest of the embryo (or of the person who will result from the embryo). If I were an embryo I would prefer to be in the lottery proposed by the thought experiment, to being used in 'destructive' research to improve culture conditions in the context of an IVF treatment.[56] Moreover, in IVF treatments the embryos are not always instrumentalised for reproductive purposes. They are also-and often solely-used as a means to other ends. Spare embryos are created to protect women undergoing fertility treatment against the risks of hormone treatment, and research embryos are used in investigations that aim at increasing safety and efficiency in freezing procedures.

4.6. Harm/omit to benefit

Another argument of defenders of DCD is that embryos can be instrumentalised for reproduction because it prevents harm to actual infertile women who undergo fertility treatments, while, in the case of stem cell research, embryos are sacrificed only for the benefit of unidentifiable people who might be benefited by stem cell therapy, but whom we do not harm now by not doing so. Infertile women will be made worse off than they would otherwise be, whereas sick people will be made better off than they would otherwise be. The underlying principle is that the obligation not to harm is stronger than the obligation to benefit.[57] People who bring forward this argument, however, depart from the idea that infertile people will make use of fertility treatments anyhow. This paper, however, investigates the inconsistency between *normative* stands of defenders of DCD. Consequently, one has to depart from their beliefs and attitudes, namely the fact that they *accept* the creation and sacrifice of embryos to help infertile people-that is, for their *benefit*. After all, another option open for them is to oppose IVF treatments because embryos should not be created and sacrificed for these purposes (as is done by many opponents of all types of hES cell research). They would not *harm* these people; they would omit to benefit them. Their argument that embryos may not be instrumentalised for the benefit of people clearly fails.[58] If defenders of DCD oppose the creation of embryos for stem cell research, they have to argue why it is more important to benefit people with a child-wish, than to benefit ill and injured people, and this to the extent that justifies the prohibition of the latter. I do not think they have a sound argument.

5. A VIEW COMPATIBLE WITH THE REVEALED BELIEFS OF DEFENDERS OF DCD AND WITH WIDELY SHARED VALUES

I think that a view on hES cell research that also accepts the creation of research embryos for stem cell derivation is compatible with the revealed beliefs of those who now defend DCD. Defenders of DCD believe that an embryo merits special respect because of its intrinsic value, but that its potential to become a person can be weighed up against other values. There are forms of respect and deference which are less absolute and which can have gradations. The respect one has for an entity does not exclude it, provided that a meaningful argument is presented, from being used as a resource for a goal

which is believed to be important. (Research on cadavers, with the informed consent of the party in question and on the condition of respectful treatment, is entirely legitimate in most countries.) Early embryos are respected by ensuring that they are used with care in research that incorporates substantive values such as the alleviation of human suffering (in accordance with the principles of beneficence and proportionality), by guaranteeing that their potential will not be wasted (in accordance with the principle of waste avoidance) and that they will only be used if there are no less contentious means of achieving the intended goal (in accordance with the subsidiarity principle). Well regulated stem cell research that uses embryos solely created for these purposes can be consistent with these widely shared values.

6. CONCLUSION

I have argued that whatever the basis is on which defenders of DCD accord intrinsic value to the embryo, once they accept the creation and sacrifice of embryos to benefit infertile people with a child-wish, they do not have a sound reason to condemn the creation and sacrifice of embryos to benefit ill and injured people who could be helped by stem cell therapies. If we consider the revealed beliefs of advocates of DCD, it seems that in general many people have respect and concern for some kind of protection for embryos, but that these feelings can change and depend on whether or not an embryo is involved in a parental project. In other words, the value they accord to the embryo is variable and depends also on criteria external to the embryo and related to intentions of people. Creating embryos for their stem cells is commensurate with the variable moral status defenders of DCD actually accord to the embryo, and, as is the case with spare embryos, these research embryos would be instrumentalised or exploited for the benefit of other people. An approach to hES cell research that would also allow the creation of embryos solely for the derivation of stem cells would be compatible with the revealed beliefs of those who currently defend DCD, and with widely shared values, in particular the alleviation of individual human suffering.

ACKNOWLEDGMENTS

Earlier drafts of this paper were presented at:
The Third International Conference of Bioethics: Ethics, Legal and Social Issues in Human Pluri-potent Stem Cells Experimentations. National Central University, Chungli, Taiwan R.O.C.; 2002 June 29.
The IAB 7th Bioethics World Congress: Power & Injustice. Brasilia, Brazil; 2002 Dec 1.

Third EUROSTEM Meeting of project partners and invited speakers: The Ethics of Human Stem Cell Research and Therapy in Europe. Venice; 2003 Nov 22.

CSEP Senior Seminar Series. The Centre for Social Ethics and Policy. The University of Manchester, UK; 2004 March 10.

I wish to thank Shui Chuen Lee, John Harris and Charles Erin for inviting me to the above mentioned

conferences and seminar. I am also grateful to the conference participants for their interesting comments and challenging questions. Of these people, I wish to thank Jonathan Glover, Daryl Macer, Søren Holm and Ludger Honnefelder for their valuable remarks. I also sincerely thank Freddy Mortier, Tujia Takala, Julian Savulescu and anonymous reviewers for their helpful comments and suggestions.

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3 Solter et al., see note 1: 186-7.

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9 National Bioethics Advisory Commission, see note 4: iv. Commission of the European Communities. *Commission Staff Working Paper: Report on Human Embryonic Stem Cell Research.* Brussels: European Commission; 2003:9.

10 Commission of the European Communities, see note 9: 34.

11 National Bioethics Advisory Commission, see note 4: 56.

12 Health Council of the Netherlands. *Stem Cells for Tissue Repair; Research on Therapy Using Somatic and Embryonic Stem Cells.* The Hague: Health Council of the Netherlands; 2002: 46.

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14 There are of course other reasons to allow the use and derivation of stem cells from spare embryos, such as regulatory scrutiny and economic reasons (Solter et al., see note 1: 126, 153) but this paper only treats the ethical justifications underlying DCD.

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23 Health Council of the Netherlands, see note 12: 45.

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27 Reichlin M. The argument from potential: a reappraisal. *Bioethics* 1997: 11(1): 1-23.

28 Belgian Chamber of Representatives. *Bill Concerning Research on Embryos In Vitro*; 2002 Dec.

29 I only mention the 'general' interpretations of potentiality. Going deeper into the variety of other interpretations and their nuances would lead me too far from the aim of this paper.

30 See for example Simon Buckle who considers the potential to become as a specific case of the potential to produce. The former he defines as 'developmental potential': the power of an entity to undergo changes to itself. The entity preserves some form of individual identity. The potential to produce does not require that any form of identity be preserved, neither is its application limited to individuals. Buckle S. Arguing from the potential. In: Singer P. et al., eds.

Embryo Experimentation - Ethical, Legal and Social Issues. Victoria, Australia: Cambridge University Press; 1990: 90-180.

31 Ibid.

32 According to some, this inherent potential can be present not until a certain stage of development is reached. Richard McCormick, for example, considers developmental individuation at day 14 as a marker line after which the embryo has to be fully protected.

33 See for example Lockwood M. Warnock versus Powell (and Harradine): when does potentiality count? *Bioethics* 1988; 2(3):187-213. See also Reichlin M. who states that the nature of the embryo is decisive: it possesses from the moment of conception a perfect human nature. In: Wolbert W. The potentiality argument in the debate relating to the beginning of personhood. *Hum Reprod Genet Ethics* 2000; 6(2): 19-26.

34 See for example Hare's argument of 'possibility for future change'. Hare R.M. *Essays on Bioethics*. London. Oxford University Press; 1993: 85.

35 Singer P. and Dawson K. IVF Technology and the argument from potential. In: Singer P. et al., eds., see note 30, 76-89. See also Buckle, see note 30.

36 See for example Noonan J.T. Jr. An almost absolute value in history. In: Noonan J.T. Jr., ed. *The Morality of Abortion*. Cambridge, Mass: Harvard University Press; 1970. See also Engelhardt H.T. Jr. who interpretes potentiality in the sense of 'probability' and proposes not to speak of "X's being a potential Y", but "of its having a certain probability of developing into Y" instead. In Wolbert, see note 33: 19).

37 Potentiality is not the only way to justify gradualism, but because the aim of this paper is restricted to the potentiality argument, it is unnecessary to mention all the other arguments.

38 Green, see note 4. Mary Anne Warren also defends a 'multi criterial' view of moral status. Warren M.A. *Moral Status: Obligations to Persons and Other Living Things*. Oxford: Clarendon Press; 1997.

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53 House of Commons Science and Technology Committee. *Developments in Human Genetics and Embryology.* Fourth Report of Session 2001-02. London: House of Commons; 2002 July 18: paragraph 18.

54 Solter et al., see note 1: 45-52.

55 Thanks to Julian Savulescu for this suggestion.

56 For this reasoning, see Savulescu, note 26.

57 Thanks to Julian Savulescu for this suggestion.

58 It is important to assess whether the approval of the instrumental use of preimplantation embryos for therapies implies the approval of pregnancy for abortion. I think it does. For an extensive analysis of this issue see Savulescu J. Should we clone human beings? *J Med Ethics* 1999; 25:87-95.

CHAPTER III
THE ROLE OF SCIENCE IN THE HUMAN EMBRYONIC STEM CELL DEBATE

PAPER 3
WHAT'S IN A NAME? EMBRYOS, ENTITIES, AND ANT*ITIES* IN THE EMBRYONIC STEM CELL DEBATE

Adapted from:
Devolder, K. What's in a name? Embryos, entities and ANTities in the stem cell debate. *J Med Ethics*. 2006(32)1:43-8

1. ABSTRACT

This paper discusses two proposals to the US President's Council on Bioethics that attempt to overcome the controversial issue of killing human embryos in human embryonic stem (hES) cell research and argues that neither of them can hold good as a compromise solution. I will argue that (1) the groups of people for which the compromises are intended neither need nor want the two compromises, (2) the US government and other governments of countries with restrictive regulations on hES cell research have not provided a clear and sound justification to take into account the views on the protection of human embryonic life of one particular group to such a considerable extent as to constrain freedom of research, and (3) the best way to deal with these issues is to accept that many people and most governments adopt a gradualist and variable viewpoint on the human embryo, which implies that embryos, under certain conditions, can be sacrificed for good reasons, and to try to find other, less constraining ways to take into account the views on the moral status of the embryo of some citizens. Finally, another, more efficient and time and money-sparing compromise will be proposed for those who accept IVF, a majority in most societies.

2. THE ETHICAL DILEMMA IN EMBRYONIC STEM CELL RESEARCH

Stem cells are widely believed to represent one of the greatest promises for medicine and biomedical research in the coming century with hopes raised for treatments for common diseases and conditions, including neurological disease or injury, diabetes and myocardial infarct. At present there are three main lines of stem cell research: on stem cells originating from early *in vitro* embryos, left over from infertility treatment or especially created for research through in vitro fertilisation (IVF) or somatic cell nuclear transfer (SCNT); on cord blood derived stem cells; and on stem cells from more developed tissues or organs from fetuses or organisms after birth. There is a growing consensus among scientists worldwide that all these lines of research are promising because the different types of stem cells may have different qualities and might be useful for different purposes. So rather than opting for one line of research, the ideal research strategy would be to simultaneously proceed with research on all types of stem cells.[1]

However, hES cell research, which at the time of writing involves the destruction of human embryos, is opposed by those who regard the embryo as in some important sense 'one of us'. For those who take this view, the embryo should never be used as a mere means, even if this could save millions of lives.[2] They advocate the legal prohibition of stem cell research that involves 'killing' human embryos.

This is the principal ethical dilemma in hES cell research: on the one hand there is growing consensus that hES stem cells uniquely hold promise for some therapies and certain types of research that other types of stem cells cannot provide; on the other hand there is the controversial issue of 'killing' human embryos in order to obtain hES cells.

3. LOOKING FOR A 'HAPPY MEDIUM' IN THE STEM CELL DEBATE

The debate over the ethics of different types of stem cell research has quite unprecedented importance. Not only because stem cell research will have an enormous impact on almost all aspects of medicine, nor because the stem cell debate combines many of the most contentious biomedical issues ever discussed. What makes this debate both unprecedented and so interesting is that compared to other areas of debate, including abortion and assisted reproduction, stem cell research is of great interest to a much larger section of society. Everyone may potentially benefit from the fruits of stem cell research: all citizens who can become patients in need of treatments based on stem cell research, the research community, the pharmaceutical industry, politicians, and many more. All of us are stakeholders in stem cell research.

This has remarkable consequences for the course of the debate. Most governments opt for a middle-position and do not want to block hES cell research, but want at least some research to proceed. (In Europe, Austria, Ireland, Lithuania, Norway, Portugal and Slovakia are the only countries that prohibit all hES cell research Austria does not explicitly prohibit the import of hES cells. Germany and Italy prohibit the procurement of hES cells but allow the importation of hES cells). [3] Probably never before in medical ethics, have governments been so creative in finding such a variety of compromise positions. Some countries, for example, believe to have found a compromise solution in making a moral distinction between the *use* of hES cells for research and their *derivation*, a process considered immoral because it involves the 'killing' of embryos. Other countries legalise the use of leftover IVF embryos for research, but not of embryos created solely for research purposes. And in both intermediate positions we find variations, for example, restricting the use of hES cells to those derived before a set date in order to avoid moral complicity with the stem cell derivation process (as in the US and Germany).

However, these compromises have satisfied few people. Neither those who think the embryo can be used for important research, nor those who say the embryo is one of us and should never be used merely as a means in research and therapy can accept the situation and they are lobbying to change regulations.[4]

The most controversial ethical questions concerning the use of hES cells would be bypassed if it became technically possible to produce cells equivalent to hES cells, without killing human embryos. This has involved science in medical ethics in a different way: science has engaged itself in trying to solve the moral dilemma in hES cell research. There have been various proposals for possible techniques of harvesting hES cells without instrumentalising human embryos, most of which I will discuss below. Last December, two new proposals presented to the US President's Council on Bioethics became the subject of discussion and offered new hope to find a way out of the moral dispute on hES cell research.[5] This paper discusses both proposals and argues that neither of them can hold good as a compromise

solution. I will argue that 1) the groups of people for which the compromises are intended neither need nor want the two compromises, 2) the US government and other governments of countries with restrictive regulations on hES cell research have not provided a clear and sound justification to take into account the views on the protection of human life of one particular group to such a considerable extent as to constrain the freedom of research, and 3) the best way to deal with these issues is to accept that many people and most governments adopt a gradualist and variable viewpoint on the human embryo, which implies that embryos can be sacrificed for good reasons, and to try to find other, less constraining ways to take into account the views on the moral status of the embryo of some citizens. Finally, another more efficient and time and money sparing compromise will be proposed for those who accept IVF, a majority in most societies.

4. TWO SCIENTIFIC PROPOSALS: A WAY OUT OF THE ETHICAL DILEMMA?

4.1. Organismically dead embryos

4.1.1. The proposal

A first compromise solution was proposed by Dr. Howard Zucker and Dr. Don Landry, both from the College of Physicians and Surgeons at Columbia University in New York.[6] Their proposal involves the possibility of deriving hES cells from no longer living embryos. They see 'death' as the common ground for disagreements about when a human being is a person because, as they say, "the death of the human being subsumes the death of the human person and so whatever disagreements about the origin of a new person, with the death of a new human being that issue of person is also resolved". They propose considering an embryo as dead when its cells have irreversibly stopped dividing, which is comparable with the standard definition of death, namely the complete irreversible loss of integral organic functioning. In both cases the human being is what they call 'organismically dead', but not 'thoroughly dead', which implies that their organs or stem cells are still alive and, in most cases, can still be harvested. According to Landry and Zucker, the procedure of harvesting stem cells from an organismically dead embryo can be compared with the donation of vital organs from a brain dead individual with consent of the next kin, which is accepted in most societies. The idea is that this application could offer a framework for hES cell research that at the same time maintains respect for human dignity *and* can advance biomedical research.

4.1.2. The target group

To consider the 'Landry-Zucker proposal', we should first ask ourselves for which group of people this compromise solution is intended? As we know that if this procedure were to become widespread the principal source of these organismically dead embryos would be embryos left over from infertility

treatments,[7] we can conclude that it is meant for a group of people that already accepts IVF but does not accept the use of living spare IVF embryos for stem cell research. These people think that the fact that an embryo has no chance to develop or is destined to be discarded anyway, does not justify the killing of that embryo since they believe there is a relevant moral difference between the lack of chance to develop and the deliberate killing of those who are 'one of us' for the purpose of research. The latter is considered as instrumentalisation of human life, which, according to some, violates human dignity.[8] Some compare it with the harvesting of vital organs from a terminally ill patient or from a prisoner sentenced to death without that person's consent.[9]

4.1.3. Does the proposal succeed in its aim?

Does the Landry-Zucker compromise overcome these objections to hES cell research? On first sight, the answer seems to be yes. The embryo is not killed for the purpose of research, so there is no question of instrumentalisation. However, we need to look not only to what people *say* that they believe, that is, to their 'professed' beliefs, but also to what may be their actual beliefs revealed through their actions. As the organismically dead embryos would be embryos left over from fertility treatments, the people for whom the compromise is meant must accept IVF. IVF is a practice in which embryos are exposed to high risks. Embryo sparing techniques are rarely used and the freezing procedure subjects embryos of good quality to a high risk of destruction.[10] Moreover, IVF involves the deliberate creation of hundreds of thousands of spare embryos that will die and countries where IVF is common practice do not put effort into promoting embryo adoption for couples in need of donor embryos, a practice which is even forbidden in some countries that allow IVF. Consequently, we can say that IVF entails the deliberate creation and sacrifice of embryos for the benefit of infertile people.[11] If people accept the creation and sacrifice of embryos to help infertile people, why would they *not* accept the creation and sacrifice of embryos for the benefit of thousands, maybe millions of people who could be helped by stem cell treatments? I have argued elsewhere that they would not have a good reason.[12]

4.1.4. A redundant proposal

If we take these implications of accepting IVF into consideration it seems that the Landry-Zucker proposal is a redundant compromise in the sense that it is meant for a group that already accepts IVF, and thus the creation and sacrifice of embryos for the benefit of infertile people. If they accept the sacrifice of embryos for the benefit of infertile people, they have no good reason to oppose the use of living left over IVF embryos for an equivalent moral purpose: the benefit of people in need of therapies based on hES cell research.

*4.2. ANT*ITIES

4.2.1. The proposal

The second compromise proposal to the President's Council on Bioethics (PCBE) came from Council member William Hurlbut, consulting professor in medical biology at Stanford University and

opponent of embryo research. His proposal involves the harvesting of stem cells not from dead embryos, but from what he has called 'embryoid-like entities' that were never alive as embryos in the first place. He proposes to produce these entities through what he calls 'altered nuclear transfer' (ANT), which involves the genetic alteration of the donor cell so that, when introduced into an enucleated egg, the resulting entity starts dividing but lacks the capacity to develop into an embryo. The idea is that destroying such entities to harvest stem cells does not raise moral concerns, since they are not embryos. Hurlbut stresses that the crucial feature of this proposal is the 'pre-emptive nature' of the intervention - the genetic alteration is done right from the start, that is, before an embryo comes into being.

4.2.2. The target group

Again a useful question is: for whom has this proposal been developed? The proposal aims to satisfy those people who oppose the killing of human embryos, whether for research purposes or for IVF. In their opinion, killing an embryo is like killing an innocent person and cannot be justified by any allegedly desirable consequences. This is the official viewpoint of the Roman Catholic Church and is shared by many pro-life and anti-abortion movements.

4.2.3. Does the proposal succeed in its aim?

Does the Hurlbut proposal overcome their objections? A first impression is (again) yes; no embryos are killed. However, a question that arises is whether the entity resulting from ANT - I have called it an ANTity - is actually an embryo or not.

During the PBCE meeting it was asked whether we would not be simply creating disabled embryos programmed for an early death. Suppose if you could, through some technique, produce an entity which had the capacity to implant but would absolutely not develop beyond eight weeks; would that procedure differ from Hurlbut's proposal? Would we not in both cases be talking about an entity that appears to be growing normally but lacks the capacity to continue that development beyond a certain point? Richard Doerflinger, from the US Catholic Bishops, stated that it is not enough to say the genetic defect was introduced into the genome from the very beginning, because: "any adult developing Huntington at the age of 40 had the genetic defect *ab initio*". It also matters what development has taken place in the meantime.

From the discussion during the PCBE meeting we can conclude that doubts are raised about the moral status of ANTities. But Hurlbut is enthusiastic and writes that: "this proposal shifts the ethical debate from the question of *when* a normal embryo is a human being with moral worth, to the more fundamental question of *what* component parts and organized structure constitute the minimal criteria for considering an entity a human organism."[13] It is doubtful whether the last question will be more easily answered than the former.

Let us go deeper into the issue of "what component parts and organized structure constitute the minimal criteria for considering an entity a human organism".
Hurlbut sees an embryo as "an engaged and effective potential-in-process". He says that "in both constitution and conduct, the zygote and all subsequent embryonic stages differ from any other cell or tissues of the body because they contain within themselves the organizing principle for the self-development and self-maintenance of the full human organism". Hurlbut seems to place the value of a human organism on its potential for further development as well as on structure, more specific, on the current state of development and proximity to the human form. According to Hurlbut, an ANTity is not an embryo but a "limited cellular system that is biologically and morally akin to a complex tissue culture". He compares it with creating parts of the whole and says that an ANTity will never rise to "the level of integrated organismal existence essential to be designated human life with potential". Therefore the harvesting of stem cells of ANTities should not present an ethical problem for those opposing human embryo research.[14]

First of all, we have to ask ourselves what the concepts 'level of integrated organismal existence', 'a self-sustaining and harmonious whole', and so forth actually mean. As Melton *et al* noted, the concepts Hurlbut uses are not well defined and have no clear biological meaning.[15]

Let us apply these terms to entities we already know and have tried to define in the past.

Defective embryos in sexual reproduction
A first example of 'partial generative potential' and to which Hurlbut refers to in his paper are defective embryos in sexual reproduction, that is those who are spontaneously aborted due to either genetic (such as abnormal chromosome complements) or epigenetic (such as defects in imprinting) defects. Hurlbut argues that ANT proposes the artificial construction of such cellular system mimicking these natural examples.

Parthenotes
What about parthenotes, that is, cleaving eggs activated without being fertilised by sperm and that did not undergo meiotic reduction? Hipp and Atala argue that: "since a parthenote is analogous to a mature ovarian teratoma [...] the *de facto* acceptance of experiments using teratoma tumor tissue lends some legitimacy to experimentation on parthenotes".[16] Kiessling and Anderson argue that primate parthenotes undergo developmental arrest *in utero* and are therefore not really embryos.[17] Hurlbut shares these opinions. The fact that parthenotes could possibly develop to the morulae stage and possibly even to the blastocyst stage[18] seems not to change his opinion. However, according to De Wert and Mummery parthenogenesis is not an 'embryo-saving' strategy because parthenotes undergo the first divisions normally. They regard a parthenote as a 'non-viable embryo'.[19] A representative of a UK pro-life group said that "human eggs have 'the potential for life' - and fertilised ones certainly do. Fertilising them in a different way, or waiting for the embryo to lose its viability, may make you

feel better about not 'killing' it, but it is as much a tampering with life as embryo research is".[20] This comment would also apply to ANTities.

Chimaeras of human nuclear material and animal oocytes

In 1998, ACT announced that it had transferred nuclei from human somatic cells into enucleated bovine oocytes to form what they called a 'pre-embryo' that, in theory, could have served as a source of hES cells.[21] Doerflinger's reaction at that time was that the relevant question is whether the resulting hybrid cell begins, even for a brief time, to grow and develop as an early human life form and that if this is the case, then this technique requires creation and destruction of human embryos.[22] De Wert and Mummery, again, do not see this as an embryo-saving technique. They consider a human-animal chimera as a human embryo since the entire nuclear DNA is human,[23] which would also be the case with ANTities.

Fertilised eggs in the pro-nuclei stage

Germany allows the cryopreservation of fertilized eggs only in the pronuclei stage. The argument is that an embryo is not formed before the fusion of sperm and egg pronuclei, which restores the numbers of chromosomes that is typical for a human being. The fact that the cell is diploid can be an important criterion for moral status. In the US, the Omnibus Consolidated and Emergency Supplemental Appropriations Act for fiscal year 1999, the term 'human embryo' included: "any organism...that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells".[24] An ANTity would be diploid, and may belong to the class of entities defined as 'any organism derived by cloning'.

Defective eggs activated through SCNT

In 1999, Lanza *et al* stated that ethical controversy over hES cell research could be avoided because it may eventually be possible to modify the genome of the patient's cells before the nuclear transfer procedure, so that after 'reprogrammation', the clones would develop only into groups of specialized cells and tissues, rather than into a whole organism. For example, only into one or two embryonic germ layers.[25] This proposal closely resembles Hurlbut's proposal. However, it may suggest that the moral status of a human entity depends on whether it can develop into one or two, or all three embryonic germ layers. However, mature teratomas can generate all three primary embryonic germ cell types as well as more advanced cells and tissues. And, as Hurlbut said about teratomas during the Council's meeting: "these chaotic disorganized and non-functional masses lack entirely the structural and dynamic character of organisms."[26]

Defective embryos created through genetic modification of ES cells

More than five years ago, Alan Trounson proposed the genetic modification of an embryo so that it can never form a placenta by inserting trophoblast inhibitor genes into, or to knock out genes from, early embryonic cells so that these cells could never form a placenta. These cells would be changed

from totipotent to pluripotent cells.[27] Is this creating handicapped embryos or creating cellular structures similar to teratomas?

'Normal' embryos
Blastocysts created *in vitro* are 'partial generative potential', but become disorganized structure when not embedded in the appropriate environment, and lose the organisational requirements to be designated human life with potential.

4.2.4. The difference between embryos, entities and ANTities

This sample of opinions on entities, embryos and ANTities may be sufficient to illustrate the difficulties in resolving the question: what makes the difference between a cellular system, an embryo and a human being? Hurlbut's criteria for considering an entity as a human embryo are unclear and not well defined. Even if an answer will be based on specific biological processes, ultimately it will still be based on normative value judgments. Of course science can influence these judgments. As Doerflinger writes "the early embryo was once dismissed as a mass of interchangeable and undifferentiated cells [...] and largely formless until the appearance of the 'primitive streak' at around fourteen days (*hence without special orientation*)" [author's italics] and "in the eighties many Catholic thinkers, *on the basis of what scientists then said*, believed there was a qualitative difference between the embryo less than 14 years old, which was then called a 'pre-embryo', and all subsequent stages of development"[28][author's italics]. There has been a tendency to try to change people's understanding of the experimental subject of embryo research. Hurlbut's proposal seems to be another attempt. The critique has been expressed that it is a semantic issue and not a scientific one.[29] Could it be that some opponents of the instrumentalisation of embryos slightly change their ethical viewpoints with regard to prenatal stages of human organisms because of the specific demands and the promising prospects of the actual research direction and hope science can provide the right and 'objective' justification?

Science *alone* will not resolve this moral dilemma. This is also illustrated by the fact that the uncertainty about the moral status of the previously mentioned range of entities has led many people to accord the benefit of doubt to embryo-like entities, and to protect them as *if* they were persons. In reaction on the first human-rabbit embryos created in China an opponent of embryo research said: "I would be wary of immediately assigning chimeras to such a sub-human status. Perhaps chimeras would be grossly deformed, or would somehow lack 'normal' human capacities, but they are created from human beings by human beings, and we should probably accord them the benefit of doubt in treating as human beings."[30]

5. FUNDAMENTAL VIEWS ON CONTENTIOUS ISSUES AND PUBLIC POLICYMAKING

Hurlbut intended to focus on the issue of overcoming the objection of people who care for full

protection for embryos. However, it is worth mentioning that there may be some other concerns that cause some people to oppose this proposal, including the genetic manipulation of human life (ANT involves interference with the cell nucleus, which contains most of the genome) and the 'slippery slope' to human reproductive cloning. It is astonishing that the PCBE is so enthusiastic about the Hurlbut proposal, which is based on the nuclear transfer technique. After all, much of US policy on so called therapeutic cloning is determined by the fear of a slippery slope to human reproductive cloning.[31] This fear has apparently disappeared like snow in summer, since none of the council members explicitly mentioned it during the meeting. Other concerns are the commodification of human body parts, and the need for eggs and the possible exploitation of women as egg donors. It would have been an interesting challenge for Hurlbut to address this latter issue. After all, the alternative sources of eggs scientists are investigating raise issues which are very contentious to opponents of human embryo research (immature eggs from aborted fetuses, human-animal chimaeras, eggs obtained through an egg-sharing program, which requires IVF, and eggs derived from hES cells[32]).

On the question why science should accommodate the fundamental views of a small number of people, the answer usually is that a democracy has to take into account minority views. But why should governments not take into account the minority views on the contentious issues the Hurlbut proposal does not overcome? One answer could be that minority views about the latter do not concern 'the most fundamental issue', namely the protection of human life, whereas the moral objection Hurlbut tries to overcome *does* concern this question. However, if governments are serious about this, why do they then not take into account the views about the protection of human life of those who oppose termination of pregnancy, or contraception that prevents fertilised ova to implant in the womb, and how about those who oppose IVF because it sacrifices those who are one of us? All these practices are tolerated by the US government, and not subjected to government control. If Hurlbut's compromise position is developed to accommodate minority views on the protection of human life, there should at least be a good reason as to why these people's view should have so much influence on stem cell policymaking, especially because the costs to society of taking into account these views are so high. Not only does it restrain scientific freedom, it also endangers public health. The burden of proof is surely on the Government; they have to justify why we should deploy so much effort to overcome their objections. As long as they do not provide such a justification, we do not have good reasons to spend so much time and effort in finding a complex compromise solution for that group of people, certainly not if we know that this delays the development of life-saving treatments for thousands maybe millions of people. As James Childress has stated with regard to US stem cell policy: "an ethical public policy in our pluralistic society has to respect diverse fundamental beliefs. And yet it must not be held hostage to any single view of embryonic life."[33] Tolerance should not go in one direction only. A minority, however vocal or vehement should not close down important options for their fellow-citizens, certainly not when it concerns fundamental right of citizens, including access to life-saving therapies. But the problem goes beyond the problem of majority versus minority. Freedom of research and freedom to pursue therapeutic options are important rights and moral values in a democracy. Of

course, scientific freedom clearly has limits. Safety and respect for research participants takes precedence over the research agenda. However, in the context of hES cell research, the application of the widely accepted principle of freedom of research depends greatly on the moral status of the embryo. A justification primarily based on a highly contested value is insufficient to restrict scientific freedom to such an extent. We should start to look for other ways to show respect to other people's fundamental beliefs on the moral status of embryos, for example by not forcing them to benefit from treatments based on embryo research or products derived from embryos.

6. ALTERNATIVE PROPOSAL FOR A 'HAPPY MEDIUM'

As Hurlbut has stated in his paper: "there is a consensus opinion in the scientific community that without NIH support for newly created ES cell lines progress in this important realm of research will be severely constrained".[34] Many scientists also claim that spare IVF embryos, although a valuable source, may not be sufficient to reach the intended goals of stem cell research. For some purposes it would be necessary to create new embryos solely for research, for example, for the study of gene and chromosomal disorders and of cell differentiation.[35]

Hurlbut stated during the meeting that a purely political solution will leave the country bitterly divided. This prompted him to look for a scientific solution of the moral dilemma. But can science alone bridge the gap between ethics and politics? I have tried to show that his compromise proposal might raise the same moral issues and disagreements as the use of stem cells from embryos, so that its intended function as a good compromise is unlikely to be realised. This is particularly the case when taking into account that the discussion and the research on the feasibility of ANT will severely postpone progress in the important area of hES cell research. The group for which Hurlbut's compromise is intended - if they are consistent in their beliefs - cannot be satisfied with any compromise on the derivation of stem cells from entities that are the beginning of human life! They can only support stem cell sources of an unambiguous moral status, such as stem cells from humans after birth. They can also not accept that some embryos will be sacrificed for research in the use of a technique that does not require the killing of embryos.

The group of people for which the Landry-Zucker proposal is intended accepts IVF. I have argued that *if* they accept IVF, they accept the sacrifice of embryos for helping infertile people. This is a viewpoint shared by those who believe the embryo should get the same protection as persons. The Sacred Congregation for the Doctrine of the Faith states that "the good intention of creating a child is not sufficient for making a positive moral evaluation of in vitro fertilization", especially because the standard by "which it is regularly practiced... involves the destruction of human beings".[36] If people accept the creation and sacrifice of embryos for the benefit of infertile people, they have no good reason *not* to accept the creation and sacrifice of embryos for an equivalent moral purpose: the benefit of people in need of treatments based on stem cell research. Moreover, this may also imply that, under certain conditions, they also accept the creation of embryos for research purposes.

One argument against this statement is that there actually *is* a moral difference between using spare IVF embryos and embryos especially created for research, because the latter have no chance of developing, into a person, whereas embryos created for the purpose of IVF do have that chance.

The compromise that might satisfy people who use this argument - if they are consistent in their beliefs - and which also might be a very efficient and less complex way to reach the intended research goals, is to create embryos solely for research purposes and to take a random selection of the same percentage of spare IVF embryos that become a human from the research embryos and donate them to infertile couples in need of a donor embryo. The percentage of 'research embryos' that becomes a human would then be the same as that of the 'spare embryos' that do so.[37] Consequently, they would have had the same chance of becoming a person. What objections could people who accept IVF have to this compromise solution? Moreover, this compromise would conserve more time and energy than both proposals put to the PCBE.

7. CONCLUSION

I have argued that neither the Landry-Zucker proposal, nor the Hurlbut proposal can hold good as a compromise solution. The world seems to divide into those who think the embryo should be protected at any price - and who, consequently oppose IVF and embryo research -
and those who think the embryo may deserve respect but lacks ultimate value and that the respect due to it can be weighed up against other values, such as the needs of people who seek genetically related children or the needs of people for stem cell treatments. The latter group's values revealed through their actions, the acceptance of IVF, would be in accordance with the compromise I have proposed here- a compromise which would be more efficient, energy and money sparing and which will be the fastest way to make progress in the 'important realm' of stem cell research. I have also argued that if a government does not take into account the minority views about the protection of human life in the context of contraception, abortion and IVF, they have no sound justification for adapting stem cell policy to minority views on protection of human life in the hES cell debate. Moreover, one group of people with a particular view on the moral status of the embryo should not close down important options for their fellow citizens, certainly when these concern fundamental rights, including access to life-saving therapies. Freedom of research is a fundamental principle and should not be restrained on the basis of a highly contested value. The best way to pass the stumbling block in stem cell policymaking is to recognize that most people accord a gradual and variable moral status to the early human embryo and accept its sacrifice for purposes considered to be of the highest importance, such as the alleviation of human suffering through the development of therapies - purposes that are as vital and important as contraception, abortion and IVF. Respect for the views of minorities, or people with a particular viewpoint on the embryo, can be shown by not forcing upon them treatments that they find unethical.

ACKNOWLEDGMENTS

This paper was presented at:
The Centre for Applied and Public Ethics, University of Melbourne; 2005 April 13
The Murdoch Children's Research Institute, Monash University; 2005 April 18

I am grateful to the people in the public for their interesting comments and challenging questions. Of these people, I wish to thank Peter Singer and Julian Savulescu for their helpful suggestions. I also wish to express my gratitude to John Harris, Lisa Bortolotti and Giuseppe Testa for their helpful feedback, which helped me to improve the paper.

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PAPER 4:
THE 'INHERENT POTENTIAL ARGUMENT' OPPOSING STEM CELL DERIVATION FROM HUMAN EMBRYOS IS FLAWED

Adapted from:
Devolder K and Ward C.M. The 'inherent potential' argument opposing stem cell derivation from human embryos is flawed. Submitted to NEJM.

1. ABSTRACT

The isolation of embryonic stem (ES) cells from human embryos has provoked passionate debate concerning the ethics of such research. One line of reasoning used to oppose the derivation of ES cells from human embryos is the 'inherent potential' argument. This states that embryos have the inherent potential to form a human and should therefore be protected as though they were a person. We argue that there is no scientific evidence to justify a separate moral status for human embryos, since the embryonic cell type that forms the mammal, the inner cell mass, exhibits identical inherent potential to ES cells. Therefore, the embryo should be viewed as a mere vehicle for the development of the inner cell mass into a person. In addition, using the inherent potential argument, we show that an embryo at the time of ES cell derivation cannot be considered an individual person. Furthermore, we demonstrate that the inherent potential argument can be used to *justify* human ES cell derivation from human embryos for use in research. We conclude that the inherent potential argument is an unsound parameter to base Government policy on human embryo and ES cell research.

2. THE INHERENT POTENTIAL ARGUMENT IN THE HUMAN EMBRYONIC STEM CELL DEBATE

The human embryonic stem cell debate has mostly concentrated around the controversial issue of using human embryos as a source of stem cells. Human embryonic stem (hES) cells offer a potentially unlimited source of somatic cells for use in transplantation therapies as well as providing a useful model system for elucidating mechanisms involved in human development and disease. One argument against hES cell research, however, is that the derivation of hES cells results in the 'killing' or 'destruction' of human embryos. For many people this is the main reason to oppose such research and in most countries it is the primary reason to adopt a restrictive hES policy.

The reason why some people object to the killing of embryos is that they consider the embryo as 'one of us'. They believe that human embryos, from the moment of fertilisation, have equivalent moral status to human persons and thus merit the same respect and protection. In their view, embryos should never be used merely as a means to other's ends, however beneficial these ends may be. There are two major arguments underlying this viewpoint. One is the official view of the Roman Catholic Church, which states that because we cannot know with certainty when ensoulment (the theological equivalent of becoming a person) occurs, we must protect the embryo from the very beginning to be certain that we do not kill an innocent human person[1]. The other argument is that we have to protect embryos from the moment of conception because from then on they are human organisms with the 'inherent potential' to become a human person; that is, they already have the genetic and organisational structure from which a person could develop. Many people who oppose the use of human embryos as a source of stem cells adopt this latter viewpoint: that an embryo is a human organism with the inherent potential to become a person and should therefore be protected as if it was a person.

Since the question of defining an embryo and which moral status to accord to it involves a normative value judgement it is unlikely that science *alone* will solve the moral dilemma in hES cell research. However, what science can do is direct these normative value judgments and point out possible inconsistencies in according moral status to embryos and embryo-like entities. We will argue that, to circumvent the problem of killing embryos, we might not need to look for complex scientific techniques for deriving stem cells, such as those recently proposed to and discussed by the US President's Council on Bioethics.[2] Indeed, we suggest that an embryo and hES cells have the same inherent potential to form a person and, consequently, people who accord moral status to the embryo on the basis of its inherent potential to form a human person should accord equivalent moral status to hES cells. Furthermore, we show that the 'inherent potential' argument can be used to both justify and oppose hES cell research, negating its capacity as a useful argument.

3. AN EMBRYO, INNER CELL MASS AND hES CELLS EXHIBIT THE SAME INHERENT POTENTIAL TO FORM A HUMAN PERSON

Several days following fertilization of an egg (oocyte) by a sperm (spermatozoon) the blastocyst is formed which consists of two distinct cell types, the inner cell mass (ICM) and the trophectoderm. The cells of the ICM and its derivative, the epiblast, give rise to *all* embryonic cells and some extraembryonic cell types. Both human and mouse ES cells are isolated from the ICM/epiblast of blastocysts. The cells of the trophectoderm only give rise to extraembryonic tissues and do not incorporate into the embryo proper.[3-5] Thus, in the early mammalian embryo there is a clear distinction between cell types that will form 'the embryo proper' and, later, the adult and those cells required for the establishment of the embryo within the uterus. Furthermore, since derivatives of the ICM form the germ cells, which subsequently produce the oocyte or spermatozoon, we can conclude that the ICM cells are the only cell type within a blastocyst that can develop into a human.

Accordingly, the embryo should be viewed as a mere vehicle for the formation of the ICM and its subsequent development into a person. This has been elegantly demonstrated in the mouse using tetraploid embryo transfer technology.[3-7] This technique uses two-cell stage zygotes to form a tetraploid embryo that acts as a surrogate trophectoderm for the ES cells. Tetraploid embryos alone cannot develop normally and do not result in an animal.[6,7] However, when aggregated with ES cells a normal fertile animal derived solely from the ES cells is formed.[3-7] The same is also true of isolated ICM encapsulated within tetraploid embryos.[6] Therefore, if the ICM can be removed from an intact embryo and subsequently be used to form a mammal, in what sense is the original embryo important? These defining experiments demonstrate that the embryo merely acts as a physical unit to facilitate formation of the developing embryo from the ICM.

Moral issues prevent these experiments being carried out in humans but there is no reason why, under

appropriate conditions, human ES cells could not form into a normal fertile person. For example, current scientific evidence demonstrates that the basic mechanism of self-renewal (the ability to exist and divide as an ES cell) is shared between mouse and human,[8-12] and this is probably true for other mammals.[13-16] Furthermore, hES cells can form the three primary embryonic germ layers: the endoderm, mesoderm and ectoderm, all essential for the normal development of a human. Indeed, hES cell xenografts in mice result in tumour-like growths that consist of complex tissue formations derived from the three embryonic germ layers.[17-18] As with mouse ES cells, the formation of these cell lineages *in vitro* and *in vivo* is dependent on the environmental cues provided, and acted upon, during the differentiation process. Therefore, it can be concluded that the inherent potential of ES cells to form lineages required for normal embryo development is the same as that of the ICM and the embryo and is identical in mouse and man.

4. SOMATIC CELLS DO NOT EXHIBIT THE SAME INHERENT POTENTIAL TO FORM A HUMAN PERSON

Some have suggested that the inherent potential argument can be used to define somatic cells (fully differentiated adult cells) as embryos, since the cloning of a somatic cell can lead to the formation of a mammal.[19] Somatic cells, however, cannot themselves form all lineages of the three primary germ layers. For example, injection of a mouse somatic cell into a mouse blastocyst will not result in the formation of germ cells derived from the donor somatic cell, whereas this does occur with ES and ICM cells. Thus, the lineage forming capability of a somatic cell is significantly restricted compared to ES and ICM cells. However, where a somatic cell has been successfully cloned the resulting entity, whether an embryo or ES cell line, will possess the inherent potential to become a person since it can form the three germ layers.

5. FROM THE INHERENT POTENTIAL ARGUMENT IT FOLLOWS THAT HUMAN EMBRYOS AND ES CELLS HAVE EQUIVALENT MORAL STATUS

Currently, the main source of hES cells are surplus frozen embryos from fertility treatment. It is widely accepted that a frozen embryo created through in vitro fertilization (IVF) exists in what is commonly known as 'suspended animation',[2] but that it is an embryo because it still has the potential to continue development once it is successfully thawed. The only condition which will realize its inherent potential is to use human intervention to place the thawed embryo within the correct environment - a womb - so that it can continue its development. But why then should we not accord the same moral status to frozen hES cells since these also have the inherent potential to develop into a human person once successfully thawed? hES cell derived trophectodermal cells could replace the role of embryos in the tetraploid method of derivation of persons from hES cells.[20] This raises the possibility that a *single* hES cell line (i.e. hES cells derived from a single embryo) could form all the extraembryonic and

embryonic tissues required for successful formation of a human person. Therefore, where a hES cell line has been successfully derived and cryopreserved it is capable of forming a person on the condition that human intervention places it in the appropriate environment so that it can continue its development. This is no different from a frozen IVF embryo; both hES cells and embryos have the genetic and organizational structure of the person into which they will develop, if implanted in an appropriate environment. That is, they both exhibit the same inherent potential to become a person. Consequently, those who want full protection of embryos because of their inherent potential to form a person should give the same protection, and thus accord equivalent moral status, to hES cells.

6. THE INHERENT POTENTIAL ARGUMENT CAN BE USED TO BOTH OPPOSE AND JUSTIFY hES CELL DERIVATION

6.1. The inherent potential argument used to oppose hES cell research

From our finding it follows that those who want full protection of embryos because of their inherent potential to form a human should accord equivalent moral status, and thus give the same protection, to hES cells. In other words, they should 'promote' the moral status of hES cells to the moral status they accord to embryos. As a result, they should view all hES cell research as 'morally wrong' since each time a hES cell is destroyed during research then its inherent potential to become a human is also destroyed. This has striking consequences for stem cell policies that allow the use of hES cells for research but not their derivation, as is the case in Germany and the US.

Federally funded researchers in the US are allowed to use a restricted number of hES cell lines that were derived before the date on which President Bush's stem cell policy decision was made public. Federal money, however, cannot be used to derive new hES cell lines. These regulations are based on a moral distinction between the use of hES cells and the preceding derivation process, which is considered unethical because of the 'killing' of embryos. A necessary condition for this distinction, which is sometimes called the use-derivation distinction, to hold true is that hES cells are not embryos, so that research on them cannot be considered human embryo research. The argument underlying this view is that since hES cells cannot develop into a human, they should not be considered human embryos. However, we have shown that the inherent potential argument can be used to assign the same moral status to an embryo and ES cells. Therefore, the use-derivation distinction argument does not hold true since hES cell research will result in the 'killing' of a cell(s) with the same moral status as a person.

6.2. The inherent potential argument in defense of hES cell research

Promoting hES cells to the moral status of embryos presents an interesting dilemma as to whether a single embryo should be seen as an 'individual organism'. A hES cell line comprises at least thousands of individual cells, all of which can be viewed as having inherent potential to form a person. Tetraploid

technology has shown that mouse ES cells isolated from a *single* embryo can independently develop into more than one genetically identical animal.[4-5] Therefore, it can be argued that a hES cell line cannot be viewed as an individual since there is the inherent potential to produce many genetically identical, yet physically distinct, persons. Furthermore, since hES cells are derived from the ICM/epiblast of individual embryos we must also conclude that both the ICM and embryo have the inherent potential to form into many distinct persons. Therefore, using the inherent potential argument, we can conclude that at the time of ES cell derivation an embryo can constitute not only one but several persons. This conclusion is corroborated by the incidence of monozygotic twins obtained from blastocysts formed by assisted reproductive technology.[21] Indeed, this is why many countries, including the UK, have adopted the Warnock report recommendation that research on human embryos be permitted up to day 14 following fertilisation, after which monozygotic twinning does not occur.[22]

Consequently, the popular argument that an embryo must be protected from the moment of conception because it is a human organism with the inherent potential to become an *individual* person can be questioned. Because an embryo has the ability to form into many 'individuals' and they are not determined at the time when ES cells are derived it follows that an individual cannot be 'killed' by the derivation procedure, whether successful or not, since the individual *does not* exist. Furthermore, it could also be reasoned that the successful isolation of a hES cell line actually saves the lives of the several 'individuals' that would not have been formed if embryo development had proceeded normally. Therefore, we now have a scenario where the isolation of hES cells could potentially save several 'persons' rather than the single individual that would be saved by preventing research on such an embryo. However absurd this conclusion may appear, it has been formed solely from the inherent potential argument that is regularly used to oppose ES cell isolation from human embryos.

7. IS THERE A COMPROMISE BETWEEN THE INHERENT POTENTIAL ARGUMENTS OPPOSING AND JUSTIFYING hES CELL RESEARCH?

Some people who accept IVF oppose the use of spare IVF embryos for stem cell research. They argue that an embryo that has no chance to develop or is destined to be discarded does not justify its 'destruction' since they believe there is a relevant moral difference between the lack of chance to develop and the deliberate killing of a 'person' for the purpose of research. Moreover, so they argue, the suggestion that the embryos are going to be discarded is misleading, "since the vast majority of embryos are not going to be 'discarded anyway', but rather would be indefinitely frozen - a problematic situation, but not the same as death."[2] Suppose we derive a hES cell line from an embryo (E). We use some of the hES cells for research and put the remaining cells back into suspended animation. The preserved ES cells still possess the inherent potential to develop into a person - genetically the same person into which E would have developed before the hES cells were derived. Whether we actually

let it develop further is irrelevant since we can freeze the hES cells indefinitely: "a problematic situation, but not the same as death". Therefore, if some of the hES cells are used for research, but others are cryopreserved for possible further development into a human person, in what sense has the original embryo (E) been killed? Its original structure has been destroyed, but certainly not its inherent potential to develop into a human person. Because its original structure as an embryo is a means to facilitate formation of the developing embryo from the ICM, there is nothing problematic in destroying the embryo structure as long as it does not destroy the inherent potential of the ICM to become a person.

Therefore, it appears that the indefinite cryopreservation of a proportion of the cells comprising a hES cell line overcomes the inherent potential argument for opposing isolation of ES cells from human embryos. However, as we have discussed above, the destruction of hES cells will also destroy their inherent potential to form a person, therefore this compromise will not be acceptable to all. Furthermore, if one accepts this compromise, or even the promotion of hES cells to the moral status of embryos, then one also has to accept that an embryo cannot be considered an individual. Clearly, this will not be acceptable to many opponents of hES cell and embryo research. Therefore, however appealing this compromise may appear it is unlikely to be accepted by countries that oppose derivation of ES cells from human embryos based on the inherent potential argument.

8. CONCLUSION

We have focused on the 'promotion' of ES cells to the moral status currently attributed to human embryos. Clearly, there is an equivalent case to justify the 'demotion' of human embryos to the current lower moral status of ES cells. Therefore, the inherent potential argument can be used to both oppose and justify all hES cell research. Supporters and opponents of hES cell research could utilise various aspects of our arguments to champion their beliefs. In our opinion, however, any argument that can justify two opposing points of view is wholly inadequate, particularly when used for the basis of Government policy. Therefore we conclude that the inherent potential argument is an unsound basis for either the opposition or justification of hES cell research.

ACKNOWLEDGMENTS:

I have written this paper together with Christopher M Ward who is working at the Centre for Molecular Medicine, Faculty of Medical and Human Sciences at The University of Manchester. We would like to thank. Cathy Merry, Daniel Brison, Sue Kimber and An Ravelingien for their helpful comments on the manuscript.

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CHAPTER IV
THE MORAL IMPERATIVE TO CONDUCT HUMAN STEM CELL RESEARCH

PAPER 5:
PREIMPLANTATION HLA TYPING: HAVING CHILDREN TO SAVE OUR LOVED ONES

Adapted from:
Devolder, K. Preimplantation HLA typing: having children to save our loved ones. *J Med Ethics* 2005 Oct; 31(10):582-6.

1. ABSTRACT

Preimplantation tissue typing has been proposed as a method for creating a tissue matched child that can serve as a haematopoietic stem cell donor to save its sick sibling in need of a stem cell transplant. Despite recent promising results, many people have expressed their disapproval of this method. This paper addresses the main concerns of these critics: the risk of preimplantation genetic diagnosis (PGD) for the child to be born; the intention to have a donor child; the limits that should be placed on what may be done to the donor child, and whether the intended recipient can be someone other than a sibling. The author will show that these concerns do not constitute a sufficient ground to forbid people to use this technique to save not only a sibling, but also any other loved one's life. Finally, the author briefly deals with two alternative scenarios: the creation of a human leukocyte antigen (HLA) matched child as an insurance policy, and the banking of HLA matched embryos.

Abbreviations: DBA, diamond blackfan anaemia; HLA, human leukocyte antigen, HSC, haematopoietic stem cell; PGD, preimplantation genetic diagnosis

2. PREIMPLANTATION HLA-TYPING

Preimplantation genetic diagnosis (PGD) has been used to enable families to have a child that is a tissue match for an existing sick sibling in need of an allogeneic haematopoietic stem cell (HSC) transplantation. HSCs are blood forming cells found in the bone marrow, the peripheral blood, and the umbilical cord blood. For several lethal malignant disorders and also for some non-malignant disorders bone marrow or blood cell transplantations are currently the only therapeutic approach.[1] The success of a transplant depends on how well the human leukocyte antigen (HLA) types of the donor and recipient match.[I]

A transplant from an HLA identical sibling is associated with a much higher success rate than a transplant from alternative donors.[2] Since all humans inherit half of their HLA type from their mother and the other half from their father, each sibling has a one in four chance of being HLA identical to one of his siblings. Given the current size of the average family in Western countries, the chance of having an HLA identical sibling is no more than 15%.[3]

The use of PGD is not a *necessary* condition for creating 'HLA matched donor children'. Before the routine use of PGD in assisted reproduction technologies (ART), there had been several cases in which a couple had had one or more children, through natural reproduction or IVF, in the hope that those children or one of them would be an HLA match for an existing child in need of a HSC transplant. Two such cases were the well publicized Ayala case and the less well known Curry case[II], in the early nineties. [4] Some sought prenatal diagnosis and were prepared to terminate their pregnancy if the fetus was not a match.[5]

I A person's human leukocyte antigen type is determined by her antigen pattern, that is, the markers on the surface of body cells and tissues. They are used by the immune system to distinguish one's own body cells and tissues from foreign ones.

Preimplantantion genetic diagnosis for HLA testing has been proposed as a *superior* method for creating a tissue matched child that can donate stem cells to its sick sibling.[6] The main advantage of this method is that it provides genetic information about embryos *prior* to implantation, so it is possible to ensure that only those embryos that are a tissue match are transferred to the mother's uterus. The couple can thus avoid the difficult decision of either terminating the pregnancy if the fetus is not a match or of extending the family, in the hope that the next child will have the desired HLA type.

In May 2004, a team headed by Anver Kuliev and Yuri Verlinsky, at the Reproductive Genetics Institute of Chicago, reported the birth of five healthy children from five different couples, created to serve as HSC donors for their older siblings affected with leukaemia, or diamond blackfan anaemia (DBA),[7] a rare form of anaemia where the bone marrow produces few, or no, red blood cells and which results in severe deterioration of normal life sustaining functions. Haematopoietic stem cell transplantation is the only possible cure. Since the leukaemia and the DBA in the affected siblings are sporadic, the matched children were *not* at risk from the same disease. This means that PGD was used *solely* for HLA typing, and not as a diagnostic technique to detect genetic diseases, for which it is normally used. One sibling with DBA received transplantation and is no longer dependent on transfusions of red blood cells, whereas the others are in preparation for transplantation or are in remission.[8]

In March, the Belgian team led by Van de Velde reported the development of a new HLA typing technique which would considerably speed up the process of HLA typing.[9] The sooner a donor match is found, the greater the success rate of the HSC transplant in the sick sibling. The study aimed at conceiving tissue donors for children affected with B-thalassaemia, but the method could potentially be used for other conditions as well where the selection of an HLA identical embryo to create a stem cell donor may be requested, including other types of cancer and other disorders of the blood cell lineage (Verlinsky *et al*,[10] p 2082). For a list of diseases treated by HSC transplants see the webpage developed by the Umbilical Cord Blood Education Alliance.[11]

Despite these promising results, however, many people have expressed their disapproval of the use of preimplantation tissue typing to have a child that can save a sick sibling.

I will address some of the main concerns of these critics and show that they do not constitute a sufficient ground to forbid people to use this technique to save the life of either a sibling, or of any other loved one.

II In the Curry case a couple in the US had a daughter, Natalie Curry, with Fanconi's anaemia. The couple decided to have another child in the hope that it would be a tissue match for Natalie. The woman became pregnant, but the fetus miscarried. After one month she was pregnant again, and a healthy baby, Audrey, was born. Unfortunately, Audrey was an unsuitable donor. Within 12 weeks the woman was pregnant again. Emily was born healthy and was a match. Twenty months after Emily's birth, cord blood was transplanted into her sister, who was then four years old. Two years later Natalie was cured.

3. MAJOR OBJECTIONS TO PREIMPLANTATION HLA-TYPING

3.1. The risks of PGD for the child to be born

Preimplantation genetic diagnosis is an established method for the diagnosis of genetic diseases, the aim of which is to prevent the implantation of affected embryos.[12] Many defenders of PGD for selection against genetic diseases are, however, opposed to PGD solely for HLA typing. They argue that an embryo and the person it will become should be exposed to the risks of PGD only if the embryo/that person is likely to derive enough benefit to outweigh these risks.[13] These risks are the as yet unknown long term effects of PGD resulting from the extraction of one or two cells from the early embryo. The underlying reasoning is that when PGD is used to test for genetic diseases that testing is done in the *best interests* of the embryo or the person it will become, whereas when PGD is used solely for tissue typing, the only benefit is for the existing sick child. Before the recent extension of the UK Human Fertilisation and Embryology Authority's policy on tissue typing,[14] the HFEA's chair, Suzi Leather, formulated it as follows: "PGD can secure an outcome, which is much better than the horrible death say, of an infant with Tay Sachs condition. Clearly then the resulting child benefits from the PGD to the extent that *it owes its serious-disorder-free life to PGD* [author's italics]. But an intervention which imposes risks without benefits, or where the benefits accrue to another person, is very different."[15]

This way of stating the objection is problematic. It is misleading to say that the child owes its 'serious-disorder-free' life to PGD. The child without Tay Sachs owes its life to PGD, in the same way as any other child selected following PGD for whatever reason owes its life to PGD. It is not as if the *same* child without PGD would have been affected by the disease. Preimplantation genetic diagnosis is not a cure, it is a selection procedure. An embryo is selected because of genetic characteristics it already had.[16] How then can PGD benefit children resulting from this procedure? For those who believe it is better to exist than not to exist (except if your life is so bad that it is not worth living), the only conceivable benefit of PGD for the resulting child is its existence, rather than a 'serious-disorder-free' existence. Without PGD it would probably not have existed at all. The parents would not have had this particular child. For those who do not believe existence is a benefit, none of the children who have come into the world after PGD have directly *benefited* from PGD. Consequently, regardless of whether you think coming into existence is a benefit or not, PGD does not benefit the child in the sense that it prevents the child from having a serious disease. The argument expressed by Suzi Leather does not hold good. Will the resulting child be harmed by PGD? We could say that one part of the procedure-the extraction of the cells-might harm the child, but PGD as a whole might nevertheless *not* harm the child if it was a necessary condition for the child's existence. This does not mean that the child could not have a complaint about the procedure. However, a child resulting from PGD for tissue typing has no more grounds for complaint about possible side effects than a child resulting from PGD for diagnosis of a genetic disease, given that in both cases PGD was a necessary condition for the children to exist. This has an important implication.

In the case of PGD for HLA typing, PGD is carried out for a clearly *person affecting* reason, namely saving an existing person-the sick sibling-whereas in the case of PGD for the selection against genetic

disease, PGD is carried out for a mainly *non-person affecting* reason, namely the creation of a new person without a genetic disease as opposed to the creation of another new person with a genetic disease. (See the non-identity problem developed by Derek Parfit.[17]) Of course we could say there will also be person affecting reasons for the latter-namely to benefit parents and society-but these kinds of person affecting reasons might also operate in the former case. The important point is that in the case of PGD for HLA typing there is an *extra* sort of person affecting reason for doing PGD, namely to save the sick child.[III] This makes the moral case for PGD for HLA typing even stronger than the moral case for PGD for selection against genetic diseases.

If one accepts the possible risks of PGD for the benefit of people who want a child, one should certainly accept these risks for the benefit of parents who want a child *and* for the benefit of a sick child in need of a transplant.

In both cases, however, we should only go ahead with the procedure if we think the health risks are minimal. It seems incoherent to treat a sick, suffering child by bringing new suffering into the world. The crucial question is what amount of suffering we can risk inflicting on one person to alleviate the suffering of another person. One strategy, and I think this is a very reasonable one, is to look at what is generally accepted in society, that is, the risk we accept now in sexual reproduction. Since the introduction of PGD in 1990 more than 1000 children have been born as a result of the procedure.[18] Current studies indicate that embryo biopsy does not increase the incidence of major malformations in the children compared to IVF or intracytoplasmic sperm injection (ICSI) children, or to figures from population registers.[19] In order to introduce a control mechanism for risk assessment, families should be encouraged to participate in follow up studies.

3.2. The intention to have a donor child

It is, however, precisely this person affecting reason that is the main cause for concern for the opponents of preimplantation tissue typing to create a donor child. Richard Nicholson, editor of the *Bulletin of Medical Ethics*, says: "We are not creating this saviour sibling to be a child in its own right. We have created it-designed it-to be a source of spare parts for an existing child."[20] Nicholson continues: "Where do we draw a moral distinction between slavery...and creating what I prefer to call slave siblings".[21] Suzi Leather says we might equally call them 'spare part sisters' or 'bred to order brothers'.

These statements are problematic because they are based on the speculative assumption that donor children, or so called 'saviour siblings', are created *merely* for *instrumental* reasons-to serve as a donor for the sick sibling-and not for their own sake. It has been argued many times before that this line of reasoning does not hold good.[22]

First of all, parents have children for all kinds of instrumental reasons. Results of 'The Value of Children Project' (in 1973, before most assisted reproduction techniques were developed), coordinated by James

III Thanks to Nick Bostrom for very helpful feedback

Fawcett, indicated that one of the advantages of childbearing most frequently mentioned is the benefit for the husband wife relationship. Other frequently mentioned reasons include 'Immortality' of the individual, continuity of the family name, and the economic and psychological benefits children provide when their parents become old.[23] This is not considered to be problematic, as long as the child is also valued in its own right.

What does it mean, however, to be valued in your own right? (If you are extremely rich or talented, and people approach you because of these characteristics, does that mean they do not value you in your own right?). Suppose we express it differently, and situate the problem not in the vagueness of not being valued in your own right, but rather in terms of not being respected, loved, or taken care of in the way people expect in given circumstances. Consider, for example, adoption. It is generally expected-at least, in these times and in certain cultures-that when you make a child, you should accept that it is your responsibility to raise and educate it. (This is the basis of the 'welfare of the child assessment' in ART prescribed by the HFEA act[24]). In the Netherlands, more than 70 children are put up for adoption every year, and the rate is still increasing. Since the adoption law came into force (1954) approximately 25 000 Dutch children have been adopted out. The Dutch Birthmother Foundation serves the interests of Dutch birthmothers and aims at "breaking through the social prejudices involved in giving up a child, discussing the alternatives to giving up a child, bringing birthmothers into contact with each other and giving them support, influencing the development of policy on adopting as well as giving up a child and expressing solidarity with birthmothers in other countries".[25] From an American site for birthmothers we learn that "there are many reasons why Birthparents choose adoption: a single mother may want her baby to have two stable parents, a couple may feel they're too young or don't have the financial resources to raise a child. Others need to complete their education or are in the midst of career difficulties. Even married birthparents may feel their relationship is not stable enough for a child or they cannot care for more children."[26] It is even stated on the site that "Birthmothers are the generous women who have made a choice that will enrich a child's life and bless adopting parents with the ultimate gift of life-to be able to parent".

These claims may not represent the general opinion in society, but they show us that in human reproduction there is always a risk of abandonment. Moreover, the fact that support is provided for these birthparents, instead of-for example, punishment via imprisonment or fines, shows we think that children put up for adoption do not face prospects so awful that we should do everything we can to prevent that children will be abandoned. If we accept that there is a risk of abandonment in human reproduction, why should we forbid people to have a child to save their pre-existing child because of the risk of 'instrumentalisation' and/or abandonment?

One argument could be that the risk of abandonment would be much higher in the case of donor children because there is a difference in intention when having these children. The reasoning then is that, whereas-to continue the adoption analogy-having a child by accident and adopting it out is acceptable, the creation of a child with the intention to use its stem cells and then to adopt it out, is something very different, and ethically unacceptable. Many opponents of preimplantation HLA typing argue that although the harvesting of haematopoietic stem cells from children is acceptable, it is wrong

to create a child with this intention. For some this is a sufficient argument to forbid preimplantation tissue typing in order to have a donor child. Others are of the opinion that the creation of a donor child is acceptable *only* if the parents wanted another child anyway: they need to have a 'genuine desire to have a child'; their intention to have a child should be clearly separated from the later 'use' of the child.[27] My response to this is that first of all, these people seem to forget that plans to have children typically change according to the circumstances and experiences of childrearing. Secondly, it is extremely difficult, if not impossible, to separate the reasons that lead to the conception of a child because of a 'genuine desire for a child' from those linked to an attempt to save another child. Moreover, these critics mistakenly presuppose that the desire or the intention to have a child determines the attitudes of the parents toward the child once born. This would imply that children conceived in order to have a brother or sister for an already existing child would not be loved, which, fortunately, is not the case.

If parents were to abandon the child after they had obtained the stem cells, then, of course, it would be clear they had created the child merely for instrumental reasons and this would wrong the child. Firstly, such a scenario is most implausible. The fact that these parents make so much effort to try to save their first child suggests they are caring and loving parents and makes it very unlikely that they will treat the new baby as a 'bred to order child'.[28] What is most important in a parent child relationship is the love and care inherent in this relationship. We judge people on their attitudes toward children, rather than on their motives for having them. Anecdotal evidence from the families who have created a child as a tissue donor for their pre-existing sick child indicates that these children receive all the love and care children should get (see-for example) the article by Jablon.[29] Secondly, as pointed out before, reproduction always involves a risk of abandonment. This is not a reason to stop conceiving children. Moreover, we should always keep in mind that the potential benefits for the sick child are enormous, which could well compensate for the risks to the future child, that is, to the child to be created.

4. LIMITS: WHAT CAN BE HARVESTED FROM THE CHILD AND FOR WHOM?

Two central concerns of opponents of preimplantation tissue typing to create a tissue donor are the limits that should be placed on what may be done to the donor child in order to treat a sibling, and whether the intended recipient can be someone other than a sibling.[30]

In accepting someone as an organ donor the most crucial considerations are the seriousness of the recipient's need, the likelihood of avoiding serious complications for the donor, and the quality of the donor's consent. Of course, newborns and small children cannot give autonomous donor consent. To decide what can be done to a child created to serve as a donor we can use what has been called the 'postnatal' test (Pennings *et al,*[31]). The standard here employed is what would be acceptable if the donor child already existed. Umbilical cord blood harvest is widely accepted since it entails physical intrusions neither on the newborn child, nor on the mother. There have been discussions about

whether early clamping of the umbilical cord can negatively affect the neonate but this has been disproved.[32] Bone marrow donations from young children to siblings are also widely accepted. Harvesting vital organs from children is not acceptable in view of the risks involved for the donor child. The donation of a kidney constitutes a difficult borderline case,[33] since one can live a healthy life with one kidney, but, of course, such a life is never without risks. I will not go deeper into the very complex discussion of paediatric living organ donation in this paper, but would like to mention that one possible approach is to say that the more risk and inconvenience involved in a procedure, the closer the relationship between donor and recipient should be. A kidney donation between two young siblings would therefore be more justifiable than one between two siblings growing up in different families. The reasoning behind this is that there is a potential psychological benefit for the donor child. A very young child may later on experience gratification or, when it is not allowed to donate stem cells or a kidney, a feeling of guilt. Moreover, if the recipient is-for example, a sibling, the donor child will have the advantage of growing up in a less stressful family environment than if the sick child had died. Decisions about such complex issues should be made on a case by case basis, the costs and potential benefits should be carefully weighed up, and the parents should make the decision with the best interests of their children in mind.

The second concern of opponents of PGD/HLA typing to create a donor child is whether this technique should be available when the intended recipient is someone other than a sibling.

In the Netherlands-for example, a father with leukaemia was saved by his daughter's umbilical cord blood:[34] In the UK, the HFEA stipulates that PGD for HLA typing should not be available if the intended recipient is a parent.[35] But why not?

One possible argument for banning these techniques when the intended recipient is a parent could be that since the chance of having a tissue matched child is very small (1 in 200), the IVF/PGD treatment is futile (given the extremely low chance of a successful pregnancy *and* having a matched embryo). However, the situation might be more problematic if bone marrow is needed. Umbilical cord blood stem cells need not be as closely matched as bone marrow stem cells. The age, the health status, and the disease of the recipient are also factors that determine how closely the match needs to be. Another possible problem is that the number of stem cells that can be obtained from the cord blood is too small to treat an adult. Research is, however, being directed toward overcoming this restriction in order to extend this option to adult patients.[36]

A second possible argument is that a conflict of interests could endanger the life of the child.

This conflict of interests is also present, however, when the recipient is a sibling.[37] First of all, in the case where the recipient is a parent, it would meet the postnatal test since bone marrow transplantations from children to their parents are currently accepted.[38] Secondly, as previously said, it is very unlikely that people who make so much effort to save a sick child or another loved one, will mistreat the new child. Thirdly, in liberal countries, the decision to have children is an area of private life in which the state may only intervene to prevent serious harms. Consequently in such countries if there is no reason to think the future child will be harmed, couples requesting PGD for HLA typing in order to have a donor child should be allowed to seek the necessary treatment.

If we know there is a reasonable chance that if a couple has a baby, stem cells from the cord blood will be used to treat their desperately sick child, or any other person they want to help, I do not see any reason to refuse them PGD/HLA typing to select a matched embryo. The donor child will not be harmed by the procedure and a desperately sick person can be saved. Even when there is a chance that, at a later age, a bone marrow harvest might be needed, this procedure should be allowed. Research has indicated that the levels of pain experienced by bone marrow donors are rather low[39] and that the discomfort and psychological maladjustment experienced by the donor can be reduced through good monitoring.[40] When the burdens can be kept to a minimum, it should be up to the parents as guardians of their child to decide what can be done to their child in order to save another loved one. It does not matter whether the recipient is family or not. We sometimes have stronger emotional bonds to people unrelated to us than to family members. Therefore, we should not restrict the use of PGD/HLA to siblings, as the HFEA currently does, but instead should allow people to have children to help other loved ones as well as their existing children.

5. ALTERNATIVE SCENARIOS

5.1. Insurance policy

What should one think of the option of using preimplantation HLA typing to ensure that all of one's children will be HLA identical, in case one of them needs a transplant? This option has been presented by Pennings.[41]

On the basis of considerations related to the risks of PGD and the welfare of the donor child, we have no good reason to object. We already accept the risks of PGD in order to benefit people with the desire for a child, and the child will certainly be created for its own sake, since its use as a donor is only conditional. Creating an HLA matched child as a back up or an insurance policy may, however, be more difficult to justify because of the costs and effort required for the procedure. Preimplantation genetic diagnosis in conjunction with HLA typing is labour intensive and requires multidisciplinary collaboration.[42] The financial cost is currently very high. If PGD is used to create a child that can save its sibling, then these costs can be compared with the probable higher costs related to the use of unrelated donors or a continued programme of standard medical treatment with no prospect of a cure (Van de Velde,[43] p 706). In the case of preimplantation tissue typing to create a back up there is no such weighing up to be done. Once the procedure becomes more routine, however, the effort and costs would be reduced and this option should be reconsidered.

5.2 Banking of HLA typed embryos

A valuable option which might be worth exploring as an alternative to back ups is the banking of HLA typed frozen embryos to provide a wide range of HLA types for unrelated individuals in need of compatible stem cells or tissue. One could adopt the embryo and carry it to term so that an HLA matched child is born or one could use the embryo *in vitro* as a source of stem cells. Moreover, this option may be more acceptable for those who accept IVF but oppose therapeutic cloning.[44]

6. CONCLUSION

In conclusion, PGD for HLA typing offers the possibility of having a child that can save a sick sibling. This person affecting reason for using the procedure is not a reason to forbid the practice, but, on the contrary, constitutes a strong argument in favour of it. Since there are no indications that donor children will be harmed, and we know that some people will be saved, it would be unethical not to allow this procedure and not to explore its further potentialities. When the burdens are minimal, as is usually the case in cord blood or bone marrow donation, it should be up to the parents to decide whether their children or their future children can act as donors for a loved one. This should not be restricted to siblings and not even to family members. It should be offered to any couples who decide to have a tissue matched baby that can save someone whom they love.

ACKNOWLEDGMENTS

An earlier draft of this paper was presented at
The Fourth International Conference of Bioethics: Biotechnology, Family and Society. National Central University, Chungli and National Taiwan University, Taipei, Taiwan R.O.C.; 2004 June 25.
I wish to thank the members in the public, in particular Margaret Sleeboom and John Harris, for their constructive comments and challenging questions. I also wish to express my gratitude to Charles Erin for very helpful suggestions to improve this paper.

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PAPER 6:
THE MORAL IMPERATIVE TO CONDUCT EMBRYONIC STEM CELL AND CLONING RESEARCH

Adapted from:
Devolder, K. and Savulescu, J. The moral imperative to conduct cloning and stem cell research. *Camb Q Healthc Ethics* 2006; (1):7-21.

1. ABSTRACT

The United Nations Declaration on Human Cloning

On 8 March 2005, the General Assembly adopted the United Nations Declaration on Human Cloning[1] in which Member States are called upon to

(a) protect adequately human life in the application of life sciences

(b) prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life;

(c) prohibit the application of genetic engineering techniques that may be contrary to human dignity

(d) prevent the exploitation of women in the application of life sciences

(e) adopt and implement national legislation to bring into effect paragraphs (a) to (d)

(f) take into account the pressing global issues such as HIV/AIDS, tuberculosis and malaria, which affect in particular the developing countries.

We will argue that cloning research does not exploit women (as d implies) and does address global health problems (not as f implies). More importantly, we will argue that it is immoral to prohibit all forms of cloning (as b suggests) and that national legislation is required to ban reproductive cloning but not therapeutic cloning (and that e is too broad). This declaration fails to take account of new research into cloning and of the distinction between cloning research for the purposes of regenerative medicine (self-transplantation) and cloning research for the purposes of developing what we call cellular models of human disease. This second application is immune to virtually all objections to cloning research.[2] The United Nations should withdraw its unethical Declaration on Human Cloning. The Declaration is as immoral as it is lethal, or so we shall argue.

2. BREAKTHROUGHS IN CLONING RESEARCH

Two months after the adoption of the UN Declaration on Human Cloning, Woo Suk Hwang and colleagues of Seoul National University reported that they had successfully cloned 31 human embryos and had produced 11 embryonic stem (ES) cell lines from these.[3] The cells were cloned from body cells from patients with diseases potentially amenable to stem cell therapy, including genetic disease, spinal cord injury and diabetes. This was the most important scientific event in cloning research since Ian Wilmut cloned a sheep, Dolly, in 1997. One year ago, the team in South Korea cloned embryos from a woman's body cells, using her own eggs. Twenty embryos were of good enough quality to extract stem cells.[4].

This new research is significant for several reasons. Firstly, it is indisputable evidence of cloning of human embryos. There were some concerns that the embryos in their 2004 research were parthenogenetic in origin. These embryos are clearly clones derived from donor oocytes and nuclear DNA from patient-donors. Secondly, the research is vastly more efficient. From, 185 eggs, 129 fused nuclear transfer constructs were created and 31 blastocysts survived. About 1 in 6 eggs produced a

blastocyst. This is high in reproductive terms - only about 1 in 5 embryos become a baby. The process is 10 times more efficient than one year ago. The accelerating pace of progress in this area is illustrated in Table 1.

Table 1. Milestones in Cloning and Embryonic Stem Cell Research

1997	Wilmut et al, , cloning of a sheep from a somatic cell
1998	Thomson et al, derivation and culture of human embryonic stem cells
2004	Hwang et al, , first human embryo cloned and stem cell line developed from it- but from own egg
2005	Hwang et al, , first human embryo cloned from donor oocytes and from patients with disease or injury and successful derivation of self-compatible stem cell lines

Thirdly, it opens up two radically new avenues for developing treatments for human disease and injury, which we will describe in more detail presently. Firstly, it is proof in principle of self-transplantation. Secondly, it opens the possibility of developing human cellular models of disease.

Cloning research is advancing quickly worldwide. In August 2004, the Human Fertilisation and Embryology Authority (HFEA) granted the first license for cloning human embryos in the UK. On May 19 2005, Alison Murdoch and her colleagues in Newcastle created the country's first cloned embryo from human somatic cells.[5] Ian Wilmut also received a license to clone human embryos. The goal in all these research projects is not to use cloning as a form of assisted reproduction to create babies (what is sometimes called "reproductive cloning"), but to advance understanding of the causes and treatment of a whole range of currently incurable diseases and conditions, including neurological disease or injury and diabetes (sometimes called "therapeutic cloning" or as we prefer, "cloning for the purposes of research and therapy").

Many people, however, have expressed their disapproval of cloning research. Senator Sam Brownback, who takes a leading role in the anti-cloning movement in the U.S., said the research by scientists from Seoul National University "underscores the need for complete national and international bans on all human cloning," because "human cloning is wrong".[6] Monsignor Elio Sgrecia, vice president of the Vatican's Pontifical Academy for Life, said, "you can't kill human life in the hopes of finding medicines to save other lives. This is not a victory for humanity but a crime twice over".[7] Leon Kass, President of the U.S. President's Council on Bioethics, stated that "allowing cloned embryos to be produced for biomedical research and/or stem cell extraction is morally highly problematic. It crosses several important moral boundaries, accelerating our slide down a slippery slope (or, more accurately, jumping us off an ethical cliff) into a dehumanizing world of genetic control of offspring and the routine use of nascent human life as a mere natural resource".[8]

3. EMBRYONIC STEM CELL RESEARCH

Before we discuss the concept of cloning for the purpose of research and therapy, it is necessary to review another recent scientific advance - the ability to culture human embryonic stem (ES) cells. Stem

cells are undifferentiated or immature cells that have the capacity for unlimited or prolonged self-renewal, and, under the right conditions, for developing into one or several types of our body cells, such as liver cells or heart cells. These characteristics make them valuable means for research and therapy. Totipotent stem cells are cells with the potential to form a complete human being if placed in a uterus. They are early embryos. Pluripotent stem cells are undifferentiated stem cells with the potential to develop into any of the approximately 200 different mature cell types in the human body, but cannot by themselves form a complete human being if placed in a uterus. They can be obtained from the inner cell mass of the blastocyst or pre-implantation embryo. At this stage, the embryo is a microscopic ball of around 100-200 cells, and is only a few days old and one tenth the size of a pinhead. Human ES cells were established for the first time in 1998[9]. Since then, the interest in ES cell research has increased significantly and, worldwide, researchers are investigating their potential and how to control their differentiation to specific types of body cells. Mouse ES cell lines have been induced to differentiate in vitro into a variety of cell types, including cardiomyocytes, hematopoietic progenitors, yolk sac, skeletal myocytes, smooth muscle cells, adipocytes, chondrocytes, endothelial cells, melanocytes, neurons, glia, pancreatic islet cells, and primitive endoderm.[10] In January 2005, a Japanese team announced that it had successfully treated monkeys with Parkinson's disease through an ES cell transplant.[11] ES cell technology has been described as the most significant development since recombinant DNA.[12]

4. CLONING

Cloning is the creation of a genetic copy of a sequence of DNA or of the entire genome of an entire organism. Although there are different cloning methods, in the cloning debate, the term 'cloning' typically refers to somatic cell nuclear transfer (SCNT). This involves taking the nucleus with the DNA code of a somatic cell (any body cell other than a germ cell) and transferring it to an enucleated egg to create a totipotent stem cell - or early embryo - capable of producing a clone or genetic copy of the entire genome from which it was derived. On February 24 1997, Scottish scientists announced that they had cloned Dolly the sheep using the SCNT technique.[13] She was the first mammal ever to be cloned this way. Using SCNT to produce live offspring is often referred to as 'reproductive' cloning. The subject of this paper is cloning for non-reproductive purposes, that is, for research and therapy.

5. THE HUMAN SIGNIFICANCE OF CLONING AND EMBRYONIC STEM CELL RESEARCH

The recent research involving cloning of human embryos is of enormous significance for humanity. Indeed, California has devoted $US 3 billion to this research. Dr. Hwang took mature cells from patients with genetic disease, spinal cord injury and diabetes, cloned them and produced 11 embryonic stem cell lines. These ES cells from patients with diseases have enormous significance for two reasons which are significantly different but currently conflated in debate about human cloning.

5.1. Self-transplantation

The first reason why this research is important is because it is a leap towards self-transplantation. The objective of what is often indicated as 'therapeutic cloning' is to produce pluripotent stem cells that carry the nuclear genome of the patient and then induce them to differentiate into replacement cells, such as cardiomyocytes to replace damaged heart tissue or insulin-producing beta-cells for patients with diabetes,[14] or virtually any cell type, including sex cells.Dr. Hwang has shown that one day we may be able to take a skin cell from a patient with diabetes, clone it, derive ES cells, produce insulin producing cells from these and transfer the resulting cells back as a transplant. Because the cells would come from the patient, as in Hwang's experiment, there would be no need for drugs to prevent rejection, which can be lethal. Although cloning research is still in its infancy and much more research needs to be done, it may give us one day the possibility to produce 'patient matched' tissue to repair damaged organs like the heart and brain, which have no capacity for regeneration, providing radical new treatments for stroke and heart attack, Parkinson's disease and many other diseases. This is regenerative medicine. It is the holy grail of medicine.Rideout and colleagues recently reported the cure of a genetic disease using therapeutic cloning.[15] They created a mouse with the Severe Combined Immunodeficiency (commonly known as the "boy in the bubble disease"). They took cells from the tail, subjected these to the cloning process, produced ES cells in which the gene was introduced to correct the genetic defect. These were introduced back into the mouse, curing the disease. This is the proof of principle for the therapeutic benefits of cloning.

Therapeutic cloning is important for several reasons:

1. There is a shortage of tissue for transplantation. As few as 5% of the organs needed ever becoming available, with the discrepancy between the number of potential recipients and donor organs increasing by approximately 10-15% each year in the US.[16]
2. There are problems with compatibility of transplanted tissue requiring immunosuppressive therapy with serious side effects. Moreover, cloned tissue would be compatible without the infectious risks of xenotransplants.
3. The role of transplantation could be expanded to include common diseases like heart attack and stroke. After disease and injury, as occurs in stroke, the dead part of the brain is replaced by scar tissue, which serves only to maintain structural integrity. It is does not function as brain would function. It may be possible in the future to use therapeutic cloning to give stroke victims new brain tissue, with full or part functionality.

5.2. Cellular models of human disease

The second reason why cloning research is important is because it opens up a whole new avenue of medical research. It could be used to study in a radically new way any disease in a culture dish. Cloning of a single skin cell could be used to produce inexhaustible amounts of cells and tissue from a patient with a certain disease. This tissue could be experimented upon to understand why disease occurs. It could be used to understand the genetic contribution to disease and to test vast arrays of new drugs.

This would enable research that cannot be done in patients themselves or where there are too few patients to work with in case of rare genetic diseases[17]. At present, it is often impossible to safely take samples of affected cells from patients, especially those with genetic diseases that affect the brain or the heart. Ian Wilmut and his team want to create ES cell lines from embryos cloned from people with amyotropic lateral sclerosis (ALS), a currently incurable neurodegenerative condition. It is impossible to remove motor neurons from patients for study. Using cloning to create cultures of motor neurons from these patients would make it possible to investigate the cause of the disease and to test new therapies. Moreover, symptoms mostly develop after the disease has been progressing for some time, which makes the study of the cause of the disease more difficult. Cloning would facilitate this research by making it possible to monitor the progress of the disease as it develops inside the cells.[18] It would also reduce the need for human and animal experimentation because human cells and tissues, not people or animals, could be used to test new drugs.

Other areas where this form of cloning would be very useful is the study of genetic variation and its interaction with environmental factors and the study of interactions between genes and drugs; the study of early human development and the underlying mechanisms regulating cell growth and differentiation, which would provide better knowledge and control over the manipulation and reprogramming of cells within patients; and the investigation of how pathogens interact with specific cell types, which would help to understand how to use viruses as a vehicle for reintroducing healthy genes to a damaged body[19].

Most importantly, new treatments could be tested on the cells and tissues derived by cloning to test for safety and efficacy. Vast panels of potentially useful new chemotherapeutic agents could be tested, for example, on human cancer tissue without needing to extensive preliminary in animals or dangerous exposure of humans to highly experimental drugs.

These two applications - self-transplantation and the development of cellular models of diseases - mean that cloning may be viewed as a scientific accomplishment on par with splitting the atom. But it will be vastly more beneficial to humanity. It may surpass the discovery of X-rays and penicillin.

6. ACTS AND OMISSIONS

James Rachels was one of the first writers to argue that we are morally responsible and blameworthy not merely for the foreseeable and avoidable consequences of our actions, but also for the foreseeable consequences of our omissions, or what we fail to do, when we could have reasonably have acted otherwise.[20] To fail to do beneficial research can be as wrong as doing harmful research.

Imagine a scientific team, after 10 years of research, develops a cure to a disease which kills 100,000 people per year. Imagine that for one year, the team fights over who will have what fraction of the profits. As a consequence, the release of the drug is delayed by one year. Those scientists are as responsible for those deaths as if they had killed those 100,000 sick people. Now imagine an ethics committee delays release of the drug because of concern over the consent process - they are responsible for their deaths if their concerns are not well grounded and significant. Imagine now that instead the

delay is not at the completion but at the very beginning - politicians prevent the research commencing for one year on some kind of moral grounds. Unless there are truly significant moral considerations, those politicians who cause the drug to be developed one year later than it could have been, are responsible for those 100,000 deaths. To fail to develop a drug which will save 100,000 lives is morally equivalent to failing to release it. We may not be able to point to those people whose lives would have been saved but their lives are no less valuable because they are in the future or they are anonymous. Cloning research could result in treatments for common diseases like heart disease, stroke and cancer. It has a considerable potential to save hundreds of thousands if not millions of lives. Through a failure of moral imagination we may continue to hold back cloning research and be responsible for the deaths of many people who perished while we delayed the development of treatments. This research is of enormous potential benefit to humanity. This provides a strong case in favor not just of allowing cloning research, but positively supporting it through permissive legislation and generous public funding. The laws which prevent such life-saving research may be, in a moral sense, lethal.

There are, however, serious ethical objections. We will consider 5 of the strongest objections, showing this new research casts many of these in a new light.

7. OBJECTIONS TO CLONING RESEARCH

7.1. Protection of human life

The central objection to all ES cell and cloning research is that it represents the destruction of human life. At this time, it is not yet possible to extract ES cells without 'killing' embryos.

The UN Declaration on Human Cloning calls upon Member States to 'protect adequately human life' in the application of life sciences. The obvious question is what we understand under 'human life' and 'adequate protection'.

Some people believe that the human embryo is human life with the same moral value as a person. Therefore, embryos should never be used merely as a means, however beneficial the ends may be. "One may not heal by killing" said Cardinal Joachim Meisner with regard to ES cell research.[21] Others think embryos have the potential to become a person, and therefore should be protected as if they were persons.

It is not our intention to review the enormous volume of debate on the issue of the moral status of the embryo. What we do want to point out here is that cloning research allows us to understand the objection with regard to destroying human life in a different light. Many countries permit research on so called spare embryos, that is, embryos created during in vitro fertilization (IVF) which are no longer a part of a couple's reproductive plans. In his cloning research Dr. Hwang used eggs from young women who were not contemplating having children at that time (otherwise they would obviously not choose to take part in a research experiment that used their eggs). Dr. Hwang used 'spare eggs' which would have otherwise perished. It is misleading to think that there are only two alternatives: either create certain embryos solely for the purpose of research or for the purpose of reproduction.

This overlooks the fact that when the creation of embryos for research purposes becomes an issue, creation for reproduction is usually not a realistic alternative.[22] The alternative to research is to not reproduce at all. The young women taking part in Dr. Hwang's experiment were not trying to conceive at the time of the experiment and the eggs used would not have gone to produce a child if they had not taken part in the research. Instead of perishing for no reason, they were used to produce highly valuable stem cells. This research did not prevent any human beings coming into existence who would otherwise have come into existence.

Embryos may have a special moral status when they are a part of a parental project. That is why it would be wrong to destroy the embryos of a couple trying to have a child with IVF. But when a couple's family is complete or they do not want children, the value people accord to embryos often decreases. That is why society allows and in some cases requires the destruction of embryos when an infertile couple have completed their family using IVF, instead of requiring them to donate or adopt out those excess or spare embryos. And that is why the status of an embryo created for research is different to the status of an embryo created for the purposes of reproduction. Just as there are spare embryos not required for reproduction, so too there are 'spare eggs' which are surplus to reproductive needs. Dr. Hwang's experiment used spare eggs and did not interfere with the reproductive intentions of any couple.

Women are born with millions of eggs and hundreds of thousands of eggs perish during their reproductive life as they will only have a limited number of, usually one to three children. Women have a right to control their reproduction and are not obliged to have as many children as they could possibly have. These eggs would never have produced a baby. Instead of perishing for no reason, they were used to produce highly valuable stem cells.

We have argued that there is a difference between the moral status of embryos created intentionally as a part of project to have a child ("wanted embryos") and those created unintentionally or for the purposes of research ("unwanted embryos"). Yet many people will continue to view embryos as children, and so not accept this distinction. But there is another way in which cloning research could be done without using human embryos at all. We could remove nucleus from a rabbit egg. DNA of a human skin cell introduced could be introduced in a nuclear transfer procedure (cloning). This chimera of a rabbit egg and human DNA would never develop into a living being - it stops development early in embryonic development at the stage when tissues are formed. However, human embryonic stem cells can be extracted from this construct and experimented upon to form cellular models of human disease.[23] Since the entity produced would never continue development, no embryo would have been formed. This cloning research would not destroy a human embryo.

7.2. Cloning is unnecessary

Republican Senator Brownback, who introduced the Human Cloning Prohibition Act of 2003 (S. 245) in the US, stated that "human cloning is immoral and completely unnecessary. Recent advances in adult and non-embryonic stem cell research are showing that real results are being achieved without reliance on controversial human cloning technology".[24].

Adult stem cells could not be used to produce cellular models of human disease as cloning and the production of embryonic stem cell lines could. This is a critical new line of research.
Adult stem cells have been found in several tissues of the human body, including skin, bone marrow, blood, the brain, and many others. Kogler and colleagues identified human adult stem cells from the umbilical cord blood with intrinsic pluripotent differentiation potential.[25] There is a growing consensus among scientists on the great value of cord blood stem cells for transplantation. Over the last years there have been extensive discussions on which line of research is promising. Those opposing ES cell research have often stated that ES cell research was not necessary since the same research goals can be reached with adult stem cells.[26] However, work over the past 2 years has convincingly demonstrated that adult stem cells will not replace ES cells. Both cell types are different; they both have their advantages and disadvantages and will be useful for particular purposes. In some cases, combined ES cell and adult stem cell therapy might be the best option.[27] Therefore, further research is required on both cell types.

Those who are against the creation of embryos solely for their stem cells argue that we could make optimal use of existing spare IVF embryos. However, there is a limited availability of good quality spare embryos. Moreover, researchers do not have control over the genetic make-up of the cells in these embryos, which presents rejection problems if they don't genetically match the patient in need of a transplant.[28] They wouldn't have the same advantages as cloned cells for studying the causes of genetic diseases and pharmaceuticals. Scientists need to create new cells that actually have genetic diseases in order to study how these diseases affect the growth and development of other cells and tissue. Moreover, stem cells from spare embryos would not be sufficiently racially or ethnically diverse. If research purposes can be reached by using spare IVF embryos, then we should first make use of these. It is surely better to use the existing embryos for beneficial purposes than to discard them. But cloning is necessary if we are properly to extract the full potential to develop cellular models of human disease.

7.3. Slippery slope to reproductive cloning

Another objection to cloning research is that this brings us 'one step closer' to human reproductive cloning - cloning to produce babies. In his statement 'Farming humans for fun' Richard Doerflinger, of the US Conference of Catholic Bishops, said that "human cloning's slippery slope toward complete dehumanization of human beings will not stop until the US Senate passes Senator Brownback's complete ban on human cloning".29 Leon Kass, President of the President's Council on Bioethics, called for federal legislation to stop human cloning for any purpose. He stated that "the age of human cloning has apparently arrived: today, cloned blastocysts for research, tomorrow cloned blastocysts for babymaking".[30]
Reproductive cloning is unlikely to ever be safe. This is based on observation of cloned animals (mostly mice and cows) that have hundreds of genes that are abnormally expressed, in particular genes important for fetal development (so called imprinted genes). This results in abnormalities during development (95% or more of cloned embryos abort), at birth ('large offspring syndrome') or later in life (even seemingly normal mice often develop obesity, die prematurely, develop tumors compared

with controls). It has been said that there are 'biological barriers' to reproductive cloning.[31] Interestingly, cloning to produce stem cells should be safe because the genes that cause the cloned embryos to be abnormal are not important for the derivation of ES cells (there is no fetal development). In addition, the isolation of ES cells is a selection process where 'normal' cells will grow out into an ES cell line whereas 'abnormal' (not fully reprogrammed cells) will be selected against.
The response to fears about reproductive cloning is not to ban cloning altogether. It is to ban reproductive cloning.
According to Carol Tauer, of the Center for Bioethics at the University of Minnesota, the reason why the UN and the US Congress failed to pass a worldwide ban on reproductive cloning is that there is a strong link between reproductive and therapeutic cloning.[32] Most countries want to postpone a decision on whether to allow cloning research or not.
To ban cloning research because of fears about reproductive cloning is not just to throw the baby out with the bath water. It is possibly to throw millions of babies out.

It is possible to separate legislation of research from legislation of its application. The UK provides one example of a country which has successfully allowed cloning for research and therapy but has banned cloning of people. The UK's Human Reproductive Cloning Act 2001 section 1(1) says: *A person who places in a woman a human embryo which has been created otherwise than by fertilisation is guilty of an offence. The act makes it illegal to gestate a cloned embryo.*[33] The slippery slope argument is, in many cases a specious one, which is intended to conceal the lack of serious reasoning. The image of a slippery slope is misleading. If a metaphor must be used then we should speak of a staircase upon which we could descend, step by step, until we have reached a certain level. Some levels are desirable, others are not. There is no reason why we should not be able to remain on a certain level and consider calmly whether or not we want to take the next step. We could even turn the slippery slope argument on itself: if we accept appeal to the slippery slope argument, then we quickly slide down to a level at which any rational discussion becomes impossible. Either legislation is ineffective or it is effective. If it is ineffective, laws banning cloning will be ineffective, so we may as well reap the rewards of research into therapeutic cloning. If they are effective, we should ban only reproductive cloning and allow therapeutic cloning with all its potential benefits.

7. 4. Economic and social justice considerations

Stem cell and cloning research have huge economic potential. However, there remain important economic and social justice objections to this research. The research is sometimes said to be a Western luxury, which will be unaffordable to most of the world. It is unjust to devote limited resources to such research.
Indeed, the UN appears seduced by this worry. Its Declaration on Human Cloning, in its final point, calls upon Member States, "in their financing of medical research, including life sciences, to take into account the pressing global issues such as HIV/AIDS, tuberculosis and malaria, which affect in particular the developing countries".
The objection from justice is more acute in light of the following three alleged problems with cloning research.

7.4.1. Unsafe

There are numerous unanswered questions as to the control of ES cell growth and differentiation. ES cells have the potential to be tumorigenic, growing into teratomas and teratocarcinomas when injected into mice. Research is being done on this worldwide and progress is being made.[34]

Recent research shows there may be infectious and other risks, such as occurred with BSE, of transplanting such tissue back to people, when it is grown on foreign culture material.[35]

7.4.2. Labour intensive and expensive

Anne McLaren, the famous British geneticist, remarked that therapeutic cloning would probably be a realistic option only for the very rich and that "any such personalized treatment will always remain labor intensive, and hence, expensive".[36] 'Clone-ialism' is the pejorative term that extends this idea: medically advanced countries will try to exploit less advanced ones and biotechnology will facilitate this trend.[37] [38]

But current treatments and care for patients suffering from chronic diseases for which ES cell therapies may be used, are also expensive and labor intensive. Moreover, therapeutic cloning may cure these diseases and not only treat them. Therapies are also likely to become cheaper, easier and accessible to more people after some time.

The whole cloning procedure takes a long time and some clinical applications may not allow for this (e.g. myocardial infarction, acute liver failure or traumatic or infectious spinal cord damage). Therapeutic cloning would likely be reserved for chronic conditions.

Apart from this, as Ian Wilmut has pointed out, "not all diseases are equal in terms of expense, and treatments could be targeted to maximize benefit. An older person with heart disease, for example, could be treated with stem cells that are not a genetic match, take drugs to suppress their immune system for the rest of their life, and live with the side-effects. A younger person might benefit from stem cells that match exactly".[39]

7.4.3. The exploitation of women

If cloning with embryos were permitted, it would require, to be effective, a large number of eggs or oocytes. In a speech of the Holy See to the UN, Archbishop Migliore stated that, "the process of obtaining these eggs, which is not without risk, would use women's bodies as mere reservoirs of oocytes, instrumentalizing women and undermining their dignity".[40]

The UN Declaration on Human Cloning also stresses this point and calls upon Member States to take measures to prevent the exploitation of women in the application of life sciences.

However, the problem of the need for large numbers of eggs from women is likely to be a short term problem for several reasons. First, one of the main purposes of cloning is to perform research to understand how cells develop and can be reprogrammed to an immature state. Once that is understood, the process can be replicated in a laboratory and there will be no need for new eggs. Second, researchers are investigating the use of alternatives, including fetal oocytes and eggs from adult ovaries, obtained post mortem or during operation.[41] In June 2005, a team of Belgian scientists

reported at the annual conference of the European Society of Human Reproduction and Embryology (ESHRE) that they had cloned human embryos using human eggs matured in the laboratory. They hope one day this will make it possible to perform therapeutic cloning by creating artificial eggs from patients' body cells. Another alternative is the differentiation of ES cells in culture into germ cells and full-grown oocytes.[42] [43] Scientists from the University of Sheffield stated at the ESHRE conference that human ES cells can develop into primordial germ cells - the cells that eventually become eggs or sperm. Recent studies have found that mammals may continue to produce new eggs throughout their live. If 'ovary stem cells' really exist, this could make it possible to produce more eggs[44]. Another option researchers are investigating is the use of non-human oocytes such as rabbit or frog eggs, for the purpose of cloning research.[45] Another possibility is to ask people undergoing IVF to donate one or two of their eggs. These women undergo the risk of hormone stimulation anyhow. The research team at the University of Newcastle upon Tyne has received permission to ask IVF patients to give up two eggs from each batch collected for their treatment.

Of course, if self-transplantation is perfected, families, eager to help their dying or sick relative, may well volunteer sufficient eggs for the treatment of their sick relative.

7.4.4. Is cloning research unjust?

These three considerations have led some to suggest that it is unjust and wrong to do cloning research. As we have alluded, each of these specific objections may have solutions in future. But most importantly, none of these considerations applies to the second application of cloning research: to provide cellular models for human disease. This will enable research into and the development of drugs to treat common diseases, like cancer and heart disease, which afflict people all over the world. These drugs may be inexpensive. Concerns about infection and safety do not apply to this research as it is about understanding disease and developing drugs in laboratory where there would be no chance of infection. It is not labor intensive - it is experimenting on cells and tissues which is done now in animals. It would not require large numbers of eggs as a few eggs would produce inexhaustible amounts of tissue to study a particular disease, since embryonic stem cells produce immortal cell lines. In so far as these objections have force, they only have force against cloning for self-transplantation, not cloning for developing cellular models of human disease.

7.5. Disruption of the moral fabric of society

There are concerns that this research is moving too fast and the community is not ready to accept it. People in society hold different values and these differing values must be respected. Concerns that moral fabric and cohesiveness of society will be torn apart provide reasons for care and reflection. But precaution must be balanced against delay in developing life-saving treatments. We must remember that many innocent children and adults are at stake. We believe that an understanding of the differences between reproductive cloning and cloning for the purposes of

research and therapy, if properly understood, would allay the concerns of many citizens. Moreover, understanding the concept of cloning to produce models of human disease, to test new treatments, should convince some of the legitimate scientific merits of this research. Further strategies to promote community acceptance and cohesiveness include:

1. Transparency. High quality, clear information about the research and its limitations. The public must understand the science.
2. Public Control and Predictability. People fear that scientists are opening Pandora's box. There must be some predictability and sense of control over the research.
3. Legislative Control. Related to 2, bans on reproductive cloning are required to achieve control over the application of this research.
4. Independent Oversight. Apart from legislation, the public may require independent oversight of scientists, through ethics committees of licensing bodies such as the HFEA and the Embryonic Stem Cell Research Oversight (ESCRO) committee proposed by the National Academy of Sciences in their report 'Guidelines for Human Embryonic Stem Cell Research'.[46]
5. Review. The field is rapidly evolving and there is a need to frequently review the adequacy of controls.
6. Participation and respect for value diversity. Individuals and cultures have different values. It is important that those different values be respected through giving individuals and particular cultures a voice, and formulating the research in light of those concerns.
7. Reassurance and Demonstration of Benefit. People need reassurance that the risks are being managed and that benefits are occurring. Most importantly, the public needs to see that these benefits are returning to citizens.

8. CONCLUSION

There are good reasons to pursue cloning research. There is potential to immeasurably increase scientific understanding of cellular development and control. There is the potential to revolutionize the practice of transplantation medicine which may significantly prolong human life. Understanding the two different applications of cloning - self transplantation and the development of cellular models of disease - helps us to address many of the objections. Cloning to produce cellular models of disease would require relatively few eggs to produce vast amounts of tissue for the study of disease. This may result in the development of drugs for common conditions which afflict people all around the world, including in the developing world. And finally, there would be no risk of infection from drugs developed by studying tissue in this way as the drug molecules would be produced pharmaceutically. Cloning research can be pursued using spare eggs which would not interfere with reproduction. Using animal eggs, oocytes grown in the laboratory, or stem cell derived eggs would avoid the problem of egg shortage entirely.

The critical point is that we cannot predict in advance the results of scientific research. What this research turns up may be very different to what is promised. But it may be very important nonetheless.

There is an important distinction between the regulation of research and the formation of social policy and law. Research should only be prevented if it harms people or exposes them to unreasonable risks. This research does not harm any person. It only stands to benefit people. We must do the research, then form the policy on the basis of the results, not in advance of them, not in prediction of them and not in fear of them. Scientific research is like trying to pick the winner of a horse race. There can be favorites, but one can never know in advance which horse will win. The race has to be run.

Just as we were able to co-ordinate nations all over the world through the Human Genome Project, we need a Cloning and Stem Cell project, where all governments facilitate this research and scientists co-ordinate, sharing knowledge and stem cell lines, to bring treatments to people quicker. We need global co-ordination of research which involves universal bans on reproductive somatic cell cloning, and scientific co-ordination that facilitates research. When it comes to research into lethal diseases, time is not only money, it is human lives. Sometimes many human lives.

The United Nations must immediately retract its misguided and immoral Declaration on Human Cloning before it consigns many more future people to early and avoidable suffering and death. Twenty-one nations in Europe prohibit cloning research.[47] Declarations, laws and policies that prevent or retard this research may prove in the future to have been a death sentence to our children. All countries must work towards a universal ban on human reproductive cloning. But equally, they must all work together to facilitate and encourage cloning for the purposes of research and therapy.

ACKNOWLEDGMENTS

I have written this paper together with Julian Savulescu, Uehiro Chair in Practical Ethics at the University of Oxford and Director of the Oxford Uehiro Centre for Practical Ethics. I wish to acknowledge the stimulus and support of the European project "CLEMIT: developing an operational ethical framework to analyse and monitor the ethics of creating and redesigning human beings", sponsored by the European Commission, DG-Research as part of the Science and Society research programme - 6th Framework, in the preparation of this paper. We are also grateful to Norman Ford and Carolyn Cameron for their helpful comments on an earlier draft and to Konrad Hochedlinger for advice.

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CHAPTER V
CONTENTIOUS MORAL ISSUES AND STEM CELL POLICY

PAPER 7:
THE PRINCIPLE OF COMPLICITY AVOIDANCE IN U.S. STEM CELL POLICY

Adapter from:
Devolder K. The principle of complicity avoidance in US stem cell policy. Submitted to *Bioethics*, under review.

1. ABSTRACT

President Bush's stem cell policy is primarily justified by the avoidance of moral complicity in 'killing' human embryos. This paper focuses on the question as to whether the primacy of 'the principle of complicity avoidance' can be a persuasive ethical basis for US stem cell policy. First, I will argue that in a pluralistic democracy the government cannot justly deny support to an area of research that holds great potential to improve and protect its citizens' health, merely because a particular group in that society objects to it on the basis of a highly contested value. Secondly, I will argue that current US stem cell policy does not succeed in what it aims for, that is, avoiding moral complicity. Consequently, the primacy of the principle of complicity avoidance is not a solid ethical basis for US stem cell policy.

2. CURRENT STEM CELL POLICY IN THE UNITED STATES

2.1. President Bush's stem cell policy decision of 9 August 2001

On 9 August 2001, President Bush made his stem cell policy public.[1] The US government would allow all types of stem cell research, but only some of these would get federal funding. Priority would go to research with animal and human adult stem cells, including stem cells from the umbilical cord, as these types of stem cell research are uncontroversial. By contrast, research with stem cells originating from human blastocysts, that is, embryos of 0.1-0.2 mm and consisting of 100-200 cells, is far more controversial. Opponents of human embryonic stem (hES) cell research condemn such research because embryos used to obtain stem cells are impeded in their further development. In their view, human embryos are in some important sense 'one of us' and merit the same respect and protection as human beings after birth. Therefore, they should never be used as a mere means to other persons' ends. They believe that: "curing even thousands of persons does not justify the destruction of others, even though they are still in the embryonic state of development."[2] Because of the controversial issue of 'killing embryos' for their stem cells, the US government decided to restrict federal funding to existing hES cell lines, "where the life and death decision [of the embryos] has already been made."[3] Federally funded researchers would be allowed to make use of 64 already existing hES cell lines, which met the President's eligibility criteria and were listed in a registry of the National Institutes of Health (NIH), the main federal Agency for funding medical research. Through this policy compromise, President Bush intended to satisfy both advocates and opponents of hES cell research. He said that this policy "allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life."[4]

2.2. The primacy of the principle of complicity avoidance

President Bush's stem cell policy is based on the argument that a 'fundamental moral line' should never be crossed. The line would be crossed if US taxpayers would sanction or encourage further

destruction of human embryos. The underlying idea is that this should be avoided at any price because this would make US taxpaying citizens, including those who want full protection for the embryo, morally complicit in 'embryo destruction'.

The central question in the moral complicity argument is whether benefiting from another's wrongdoing effectively makes one a moral accomplice to their 'evil' deeds.[5] Whether one considers somebody as morally complicit in embryo destruction depends on one's view on the separation principle, which, applied to hES cell research, states that the act through which the cell products are obtained should be completely separated from the use that is made of these products. If so, then those who use or somehow support the *use* of the cells cannot be considered moral accomplices in the act of stem cell derivation. [6]

In his stem cell policy, President Bush wanted to guarantee this separation while getting the maximum benefit and therapeutic potential out of hES cell research. His policy is based on a moral distinction between *using* hES cells and the preceding derivation process, an act considered to be 'evil' by those who consider the embryo as one of us. The President defends the so-called 'use-derivation-distinction'.[7] To guarantee a *complete* separation between both acts - use and derivation - President Bush introduced the restriction of federal funding to lines created prior to his stem cell policy decision. The argument is that the 'destruction' of the embryos happened in the past so that the decision to allow the use of the already existing hES cell lines cannot have led to the destruction of these embryos. Pro-life supporters of Bush's stem cell policy have expressed it this way: "while we mourn the lives of those children that were killed to derive the sixty-plus stem cell lines that currently exist, there is nothing that we, as a pro-life community or President Bush can do to restore the lives of those children. Neither President Bush nor the federal government had anything to do with the destruction of those embryos or the establishment of those cell lines."[8] Moreover, so the argument goes, by prohibiting the use of hES cell lines created after [9] August 2001, the President's policy cannot possibly have encouraged or still encourage further embryo destruction after this date. The idea is that since the separation is guaranteed through President Bush's policy and any moral complicity with embryo destruction is thus avoided, it is ethically acceptable to benefit from the products of embryo destruction. This is the basis of current US stem cell policy.

Several authors have dealt with the issue of moral complicity in the context of hES cell research.9 Opinions on whether or not President Bush's policy actually avoids moral complicity in embryo destruction are divergent because there is no consensus on the criteria for determining whether an act of benefiting from an 'evil' and the 'evil' act itself are actually separated. Not everyone thinks that the 'fundamental moral line' would be crossed if President Bush would allow the use of spare embryos created after 9 August 2001,[10] just as not everyone agrees that his current policy does not cross the 'fundamental moral line'.[11] I will not deal with all the different positions in this paper. They have been discussed elsewhere.[12] What is relevant here is that President Bush believes that his policy allows as

much hES cell research as possible within ethical boundaries, that is, without crossing the fundamental moral line. Allowing more would mean crossing the line.

2.3. US stem cell policy under pressure

Now, four years after President Bush's decision, his stem cell policy has come under pressure from scientists, the public and, subsequently, politicians.

The public

At the time of President Bush's stem cell policy decision, a majority of Americans seemed to support hES cell research and believed such research should be federally funded.[13] Since then, dozens of polls have indicated that this support seems to have grown the last couple of years.[14] Although it is not clear to which extent we can rely on these polls,[15] we can expect that if successful stem cell treatments will be developed in more permissive countries or jurisdictions public support will increase considerably. Nowadays, it is mainly patient organisations, that is, those who are aware of the promising potential of hES cells to treat disease, which are lobbying to relax current US regulations.

Scientists

There is a growing consensus that the hES cell lines eligible for federal funding are inadequate to advance stem cell science. Of the 64 originally listed in the NIH registry (which later grew to 78), only 22 are actually available.[16] This is too few to accommodate the genetic diversity in the world population. Moreover, all NIH registered cell lines were prepared using mouse cells, which may rule them out for clinical trials because of the risk that an animal virus might be passed to patients.[17] A recent study shows that the approved cell lines share a trait that fosters rejection by the immune system, diminishing their potential as medical treatment.[18] A second study found that at least 5 of the 22 approved hES cell lines will never be useful in a clinical context because they are difficult to grow and that each colony has its own tendency to turn into a particular type of body cell, suggesting that more than the 22 colonies will be needed if hES cell research is to reach its full potential.[19] Consequently, the move towards clinics is as good as impossible with US federal money. Furthermore, US stem cell policy also restricts *fundamental* scientific research. A better understanding of the conditions or factors that govern stem cell proliferation or directed differentiation can be tested and verified only by deriving new lines and addressing whether they behave as predicted. For the study of specific diseases new hES cell lines that actually have that disease are needed. These would also be useful for drugs and toxicity testing. The Reproductive Genetics Institute in Chicago, for example, has created 50 cell lines representing 6 genetic diseases, including muscular dystrophy. However, none of these lines can be used by a US government-funded researcher. A more liberal funding plan would give federally funded scientists the ability to transcend all these limitations and to make progress in this promising area of research.

Politicians

Pressure from scientists and the public have urged politicians to undertake political measures to try to relax current US stem cell policy.[20] Even some conservative and pro-life republicans have urged Bush to extend his policy.[21]

However, last year, it already became clear that President Bush did not have any plans to relax his policy, even if he agrees that stem cell science would benefit from a more liberal funding plan. Part of a letter from NIH director, Elias A. Zerhouni, in a reply to over 200 members of the House of Representatives who had asked Bush to relax his stem cell policy, seems to indicate that the President's refusal to relax his policy now solely rests on *ethical* arguments.[22] Zerhouni wrote that "although it is fair to say that from a purely scientific perspective more cell lines may well speed some areas of human embryonic stem cell research, the president's position is still predicated on his belief that taxpayer funds should not 'sanction' or encourage further destruction of human embryos that have at least the potential for life."[23]

In May 2005, Bill HR810 passed the House of Representatives. If passed by the Senate, this bill, also known as the Stem Cell Enhancement Act of 2005, would allow federal support for research with hES cells from spare IVF embryo regardless of the date on which these where derived (in the US, approximately 400,000 embryos 'reside' in freezers[24]). This would allow US scientists to derive new hES cell lines with federal money. However, at the time of writing, it seems unlikely that Bill HR810 will pass, since President Bush intends to veto any new law extending his policy and he has repeated this statement several times.[25] He said about the bill that it "would take us across a critical ethical line by creating new incentives for the ongoing destruction of emerging human life" and that "crossing this line would be a great mistake."[26]

2.4. Relaxing the regulations means crossing the moral line

The fact that President Bush needs to 'stick to his guns' can easily be explained. It is a necessary condition for taking the ethical justification for his policy seriously. Any concession would mean crossing the fundamental moral line and would torpedo the ethical basis of his policy: the avoidance of moral complicity of US taxpayers in embryo killing.

This becomes clear if we assume that the President would relax his policy in the most obvious way, that is, with the least change. The most obvious concession would be to shift the cut-off date of 9 August 2001 to a later date so that new hES cell lines become available to federally funded researchers. The same argument used to defend his current stem cell policy could be applied to justify the new policy: the killing of the embryos could not have been induced by this policy decision and no further encouragement is possible because researchers cannot use hES cell lines created after the date of the new policy decision. Louis M. Guenin has called this the 'surprise announcement scheme':

"For some contracted period, the government declares that it will not fund any research that effects

or is consequent on destruction of an embryo. After this policy has become widely known, at some later time to the government issues a surprise announcement that it will fund research on all and only the derivatives of embryos sacrificed before to".[27]

However, as Guenin has pointed out, the surprise announcement scheme ends in complicity. If it is known or anticipated that the government will periodically advance the cut-off date; then demand by federally funded scientists will continuously induce creation of cell lines in the expectation of the next advance. [28] Consequently, President Bush can only hold on to 9 August 2001 as the only cut-off date and is forced to refuse any proposal to set a later date as borderline that cannot be crossed.

3. CONSEQUENCES FOR SCIENTIFIC FREEDOM AND THE PROTECTION OF PUBLIC HEALTH

3.1. Federal responsibility for supporting medical research and assuring freedom of research

The idea behind federal funding is that it is necessary to adequately support medical research and that it assures freedom of research for institutions as well as for individual scientists. By denying federal funding for research on newly created hES cell lines, President Bush seems to have abdicated both responsibilities.

However, two arguments could be advanced to deny this claim and legitimize his policy. A first argument is that, unlike in other countries, such as Costa Rica, Ireland and Poland, hES cell research is not *banned* in the US, at least not on the federal level. Currently, there are no limits on private funding of hES cell research and there are reasons to believe that, as John Robertson has pointed out, the "denial of government support may slow research, but, if the science is strong, there will be ample private sector incentive in the US that permits hES cell derivation to bring to market safe and effective treatments."[29] Second, states are allowed to devote taxpayers' money to hES cell research on their own initiative. In November 2004, Californian voters approved Proposition 71 which establishes a state constitutional right to pursue hES cell and cloning research, and provides $300 million a year for hES cell research for the next decade. New Jersey followed this initiative and more states are considering doing the same.[30] Consequently, the President could argue that in states where taxpayers accept and want public support for hES cell research, this will become clear through local decisions. The federal government does not prohibit or restrict such state initiatives in any way.

Do these two arguments justify the lack of federal support for hES cell research? Can we count on private and state initiatives alone to guarantee freedom of research and adequate support for hES cell research?

3.2. Freedom of research and medical progress

Federal funding is crucial for hES cell research to proceed at a high rate and for conducting important fundamental medical research with a long-term perspective, where profit is irrelevant and the progress of the science is aimed at improving and protecting citizen's health.

First, government funding places a 'stamp of approval' on this type of research. This is important a restrictive legal regime will typically discourage private funding. [31] Secondly, when federal funding is scarce and research in its infancy, which is the case with hES cell research, private companies are reluctant to invest. [32] They generally do not invest large amounts of money in basic research, but rather in applied research, especially that which aims to develop drugs and other treatments for common disease. Private companies need to make profit, and if there is no money in a certain type of research, it can be stopped, however beneficial it may be for public health or for the progress of science. Consequently, freedom of research is not guaranteed by merely not imposing any limits on private research. Moreover, medical research needs an enormous flow of money to reach its full potential and private sources alone will be unable to keep pace with the need of stem cell researchers.[33] The same counts for state initiatives. Concerns have been expressed that the economy of a single state such as California cannot support such an expensive research program, certainly not in the face of many other pressing priorities.[34] Thirdly, if most of the research is done in the private sector, they will own most patents and licences. This will slow down dissemination of knowledge (there is no pressure to publish the results) and will leave the public uninformed. Informing citizens about the work being done could gain their support for hES cell research. This brings us to another negative effect of the lack of federal funding.

3.3. Lack of federal oversight and risks for public health

By providing federal funding, the US government could increase its control over hES cell science.[35] Federally funded researchers must first get approval from a government review panel to conduct their research, whereas non-federally funded researchers only need approval of the review board within their research institution. Some private companies have set up their own ethical advisory board but concern has been expressed that this risks being more of an 'ethical cover' than ethics that can be taken seriously.[36]

In 2005, the US National Academy of Sciences (NAS) issued a 143 page report in which they provide guidelines "for the responsible practice of human embryonic stem cell research".[37] However valuable these guidelines may be, they are not legally binding and are not enforceable by the federal government. Nevertheless, through this report the NAS have exposed the shortcomings of Bush's stem cell policy. The report points out that: "because of the absence of federal funding for most current hES cell research, some standard protections may be lacking, and the implementation of protections is not uniform across the country" and that "heightened oversight also is essential to assure the public that such research is being conducted in an ethical matter".[38]

We can conclude that through his policy, President Bush has abdicated of both responsibilities: adequate support of medical research and assuring freedom of research for institutions as well as for individual scientists. The costs of the primacy of the principle of complicity avoidance in US stem cell policy are serious. They lead to slowed progress of hES research and, consequently, a huge delay in developing life-saving treatments. Even if stem cell products and therapies will be developed in the private sector, it is irresponsible to permit the widespread medical services without federal support of medical research and fundamental scientific research required to establish the safety and efficacy of these services.[39]

Keith Yamamoto, science advisor for the California Stem Cell Research and Cures Initiative, is right when he claims that Californian Proposition 71 (and thus other state initiatives) is not a model for the support of biomedical research, but rather "a stopgap measure whereby our largest state steps in to allow important work to move forward and, in so doing, perhaps reawakens the federal government to one of its most crucial mandates".[40]

3.4. A policy based on widely shared values versus a policy based on a highly contested value

Even President Bush seems convinced of the importance of federal funding for stem cell research. In his 9 August 2001 speech, he said: "federal dollars help attract the best and brightest scientists. They ensure new discoveries are widely shared at the largest number of research facilities and that the research is directed toward the greatest public good."[41] Apparently, he believes the costs to society of denying federal funding weigh less than the costs of some taxpayers paying against their will for research that they consider unethical.

There are at least two reasons to think this policy is hard to justify.

First, in a democracy, it is untenable and undesirable to have a tax system in which taxpayers are allowed to choose to which government approved programs their money should go to. This certainly applies to important scientific research that is in the interests of all citizens. We pay all the time for programs that we do not support, and sometimes we are happy when the government decides to spend federal money on a program (e.g. culture), which would probably not have been supported if people could refuse to direct their tax money to particular programs.

Secondly, and most importantly, in a pluralistic democracy, public policy should not be determined by a majority opinion alone, nor should a minority block all the options open for their fellow citizens. When important rights and values are at stake, as is the case in the decision to deny federal funding for hES cell research, the law cannot be used to impose one's, often religiously based views on the embryo to the rest of society. Intrusion upon fundamental rights and widely shared values can only be justified on the basis of other fundamental rights and widely shared values. Religiously based views on fundamental rights (e.g. the right to life of the embryo) are insufficient to restrain other fundamental rights (e.g. freedom of religion, freedom of research). The reason is that these views can

only be justified on the basis of a highly contested value, that is, the 'high' moral status of the embryo. A particular interpretation on 'the right to life' on which there is huge dissension, cannot be a fundamental right (although there is a fundamental right to defend one's own interpretation of 'the right to life').

3.5. Interim conclusion

Freedom of research is one of the most important rights and moral values in a democratic society. It is not an absolute value and can be restrained by other important values such as the protection of research participants and patients. However, in US stem cell policy the restriction of freedom of research depends greatly on one particular view on the moral status of the embryo, and certainly not on the protection of patients or research participants. A justification primarily based on a contested value is insufficient to restrict freedom of research to such a considerable extent.[42] Current US policy cannot justly deny support to hES cell research, which holds great potential to improve and protect citizen's health, merely because one particular group in that society objects to it on the basis of a highly contested value.

4. PRESIDENT BUSH IS NOT RADICAL ENOUGH

4.1. Merely denying federal funding is pursuing a permissive policy

It is astonishing that a policy that seems to be based solely on *ethical* arguments with regards to embryo protection leaves non-federally funded stem cell research unrestricted and unregulated. Merely denying federal funds for hES cell derivation is actually pursuing a permissive policy with regard to what can be done to embryos. It allows wrongdoings to continue while, hypothetically, restrictive measures could be put in place. If President Bush really wants to accommodate the wishes of those who oppose embryo killing, this is a questionable policy. Even the UK, which has one of the most tolerant legislations with regards to hES cell research, has taken more measures to protect embryos. (For example, through the Human Fertilisation and Embryology Authority (HFEA), which licenses and monitors all human embryo research).

Either President Bush does not really intend taking into account the views of those who think the embryo is one of us, which destroys the ethical justification for his policy, or he does not really believe the embryo merits protection. Let me explain by means of an analogy - one which is typically used *in defence* of President Bush's stem cell policy.

4.2. The Nazi analogy[43]

Carolyn Cargaro, a pro-life feminist, wrote in defence of Bush's stem cell policy: "those sixty embryos were destroyed specifically for experimentation, so isn't the use of the stem cell lines condoning such destruction? I do not believe so, any more than accepting treatment for hypothermia is condoning Nazi death camp experiments."[44]

In debates about moral complicity and benefiting from evil in stem cell research, reference is often made to discussions about the use of data obtained through horrific medical experiments on concentration camp prisoners during World War II. [45] The best known are those conducted by Dr. Mengele on twins, the low pressure and the Dachau hypothermia experiments (freezing experiments). In all these experiments, the victims were tortured and most of them died in anguish and pain. There has been a lot of discussion about whether it is ethically sound to cite these experiments or to make use of some of the data obtained through the experiments when this can benefit society. Opinions range from a total ban to advocacy of the uninhibited use of the data. For example, Arnold Relman, editor-in-chief of the New England Journal of Medicine between '77 and '91, categorically refused citations of Nazi data in the journal on ethical grounds.[46] Many people believe that using these data would constitute some sort of ceremony of respect or scientific acceptability of the Nazi doctors, and of disrespect towards the victims' memory. Some think that using the data is "simply a matter of choosing to ignore its immoral beginnings".[47] Others, like for example Robert Pozos, a physiologist specialized in hypothermia, have advocated the free use of the results, believing that they can advance contemporary research on hypothermia and save lives.[48] He said: "it could advance my work in that it takes human subjects farther than we're willing". Kristine Moe suggested that by using the hypothermia experimental data, 'good' would be derived from evil, but that scientists should use the data only in circumstances where the scientific validity is clear and where there is no alternative source of information.[49]

A same range of opinions, with similar arguments, exists about whether it is ethically sound to make use of the NIH-registered hES cell lines, with President Bush who believes no fundamental moral line is crossed by allowing the use of these hES cell lines on one end of the spectrum, and people like Ben Mitchell, of the Center for Bioethics and Human Dignity, who thinks that "those who destroyed the embryos are guilty of homicide [...], and that guilt passes to those who knowingly use in their research cells obtained at the expense of embryonic life"[50], on the other end.

In both the Nazi and hES cell research cases, there is wide agreement that benefiting from evil cannot have led to the killing of the 'victims' and will not encourage similar acts in the future. Causal responsibility for and direct encouragement of evil are two criteria often invoked to determine whether or not one is morally complicit in an evil act.

In both cases, however, no agreement exists on whether it is ethically acceptable to actually benefit from the evil acts.

It has been suggested that if there is wide agreement on the former, disagreement on the latter should be left to the personal level. The idea is that when past or future causation is lacking, the question of benefiting from a past evil becomes a matter of symbolic association and personal conscience, not morality and public policy.[51]

This is why benefiting from the Nazi data is not prohibited. Whether one wishes to benefit from the data is an individual choice, which can be the subject of discussions. The same arguments seem to

underlie President Bush's stem cell policy. There is wide agreement that his policy decision cannot have led to the killing of the embryos used for establishing the NIH-registered stem cell lines and will not induce further embryo killing. Further discussion is left to the personal level, or at least, not to the federal level.

Both policies are based on the primacy of the principle of complicity avoidance. There is one reason, however, why the 'Nazi analogy' is misleading.

The Nazi experiments happened more than 60 years ago. The US government has not only condemned these experiments, it has also punished those who committed or were complicit in the experiments. In 1947, US authorities held the 'Doctor's Trial' in Nuremberg, before US military courts. Of the 23 defendants that were accused of having been involved in Nazi experiments- all medical doctors- 7 received death sentences and 11 received prison sentences ranging from 10 years to lifetime imprisonment. The US government has also taken strong legal measures to prevent the experiments from ever being repeated again. The Nuremberg Code - a set of principles for human experimentation - was developed in response to the inhumane Nazi experiments and together with the Declaration of Helsinki became the basis for the Code of Federal Regulations (Title 45 Vol. 46), which are the regulations issued by the US Department of Health and Human Services governing federally funded research in the US. These actions and measures convincingly show that the US government, even if it allows the use of Nazi data, really believes the Nazi experiments are repugnant and should never be repeated again.

The same cannot be said about the government's hES cell policy. This is where the analogy fails. In the US, embryos are still used in 'unethical' or 'horrific' medical experiments; not only in the private sector but in all non-federally funded research. The killing does not happen occasionally, by some sinister medical doctors, but on an organised and industrial scale.
Apart from the 'medical experiments', embryos are routinely killed through the use of the intra uterine device (IUD), the 'morning after' pill, and abortion, even for non-medical reasons. Embryos are also being created and sacrificed for purposes regarded as beneficial, such as helping infertile people. About 400,000 spare IVF embryos 'reside' in freezers, many of which will die or be killed for beneficial experiments, or just because their conceivers have decided so. In other words, embryos are routinely being killed in the US and this is tolerated by President Bush, and by the majority of US citizens (as they are the one who make use of these practices).

Imagine that Neo-Nazis in some rogue state are still conducting hypothermia and other experiments on innocent people without their consent. The victims are terminally ill. They are going to die 'prematurely' anyway. The use of the data obtained through these experiments will lead to medical treatments for millions of people worldwide. President Bush gives a speech to make his new policy public. Federally funded researchers would be allowed to make use of a selection of the data obtained

before the President's decision. The data are accessible on the NIH website. Through this policy compromise, President Bush intends to satisfy both advocates and opponents of benefiting from these data. He says that this policy "allows us to explore the promise and potential of this research without crossing a fundamental moral line by providing taxpayer funding that would sanction or encourage further destruction of innocent people."

The fundamental moral line as determined by Bush's policy is not crossed, so complicity is avoided. But would society approve of Bush's policy and would US citizens take the argument underlying his policy seriously? I don't think so. If President Bush allows murders, but just does not provide federal funds to support them this would not be considered an adequate moral stance on the issue of murder.

4.3. Interim conclusion

Those who oppose embryo killing can only be satisfied with Bush's federal funding restrictions if his policy would at the same time condemn and prohibit all embryo-killing in the US. The primacy of the principle of complicity avoidance can only be a solid basis for US policy if President Bush follows through and does everything he can to protect embryos.

5. CONCLUSION

There is a broad consensus that hES cell research holds great potential for medical research as well as for developing therapies, and that this potential should be investigated. There is growing pressure from the American public, scientists and politicians to relax current US stem cell policy, and we have all reasons to expect this pressure will increase when successful hES cell therapies will be developed in other countries or jurisdictions. However, the President refuses any concession, as this would undermine the ethical basis of his policy: the primacy of the principle of complicity avoidance. I have argued that the primacy of the principle of complicity avoidance can only be maintained at a great cost to society, as it restrains freedom of research and leads to a lack of federal oversight and consequently, lack of protection of public health. I went on to argue that there are two main reasons why the primacy of complicity avoidance cannot be a solid basis for stem cell policy. First, in a pluralistic democracy, the government cannot justly deny support to an area of research that holds great potential to protect and improve its citizens' health, merely because a particular group within society condemns the research on the basis of a highly contested view on the moral status of the embryo. Secondly, it is hard to justify the primacy of the principle of complicity avoidance as a solid ethical basis for a policy that at the same time tolerates the killing of embryos on an industrial scale. A policy based on the primacy of complicity avoidance can only be taken seriously if it really does what it aims for: protect human embryos and avoid any moral complicity with embryo killing. We can conclude that the primacy of the principle of complicity avoidance cannot be a solid ethical basis for US stem cell policy. It is unethical to discourage potentially life-saving research by denying federal funding on the basis of a weak ethical position.

ACKNOWLEDGMENTS

I wish to express my gratitude to Freddy Mortier and John Harris for helpful comments and suggestions. I also wish to thank Isa Cossement for correcting the English.

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PAPER 8:
ADVANCE DIRECTIVES TO PROTECT EMBRYOS?

Adapted from
Devolder, K. Advance directives to protect embryos? *J Med Ethics* 2005 Sep; 31(9):497-8.

1. ABSTRACT

I have designed an 'advance directive to protect embryos' so as to offer those who think human embryonic stem (hES) cell research is immoral, the opportunity to ensure that they do not openly or inadvertently benefit from therapies developed through research that they consider evil, when it is possible for them to avoid it. The advance directive is meant to dramatise the consequences of consistently holding a particular moral view and to stimulate discussion about how the stem cell debate should proceed.

2. THE CONTINUING DEBATE ABOUT HUMAN EMBRYONIC STEM CELL RESEARCH

There is a growing consensus among scientists worldwide that hES cell research will lead to the development of therapies for common diseases or conditions that affect millions of people, including neurological disease or injury, diabetes, and myocardial infarction. hES cells also provide valuable tools for understanding early human developmental processes, for drug discovery and toxicity testing and for developing cellular models of human diseases. At the same time many individuals profess to be outraged by the prospect of using human embryos for research and therapeutic purposes and some countries or states have declared such research to be unethical and have banned it. Many people also think it would be immoral to benefit from what they consider to be 'evil'.

Obviously all those who think hES cell research is immoral will wish to ensure not only that no hES cell therapies are developed but that they will not openly or inadvertently benefit from such therapies when they can avoid it. I have accordingly designed the following Advance Directive and here offer it as a service to all those offended by therapeutic and research use of human embryos.

Advance Directive

I, ... (*name)*
Of.....
..... (*address)*am of sound mind and not suffering from any physical or mental condition which impairs my capacity to make the medical treatment decision set out in this document. I have carefully considered how I would wish to be treated if through accident, illness, or injury I lose the capacity to consent to medical treatment or the ability effectively to communicate my consent or refusal.

I refuse the following specific treatments for my condition:

Any medical treatment that is based on human embryo research or products derived from human embryos

I wish it to be understood by those treating me (and others) that my refusal of medical treatment based on human embryo research or products derived from embryos is a considered and careful decision made while I have the capacity to consent to or refuse such treatment. I am fully aware that one of the consequences of my refusal to accept medical treatment in these circumstances may be my death. I do not wish to suffer the loss of dignity which will be caused if medical treatment is given to me to which I do not consent.

GP's declaration
I have discussed the matters contained in this *advance directive*
with.....

I am satisfied that he/she has the capacity to make the decisions contained in this document and satisfied that he/she understands the consequences of those decisions.
GP's signature.....
Date of signature...../...../.....

My signature
.....

The design of this advance directive to protect embryos highlights an important point that is often overlooked, namely that those who object to hES cell research as unethical and who block such research are committed in consistency to the rejection of any benefits or therapies that may flow from such research. It is questionable whether these people will fully accept this consequence of opposition to hES cell research and whether this rejection of hES cell research will be practically possible. (Once stem cell therapies have been developed and stem cell research is conducted worldwide it will be very difficult, if not impossible, for practicing physicians to know whether a drug or therapy was or was not developed through hES cell research).

We should keep in mind that very often there is a significant difference between what people say that they believe, that is, their *professed* beliefs, and their *actual* beliefs as revealed by their actions. It does not follow from the fact that people *claim* that embryos should be protected as if they are persons that those same individuals will follow through and do everything necessary to ensure that in fact this protection is implemented. In most countries with restrictive legislation on the use of embryos, intrauterine devices, and the 'morning after' pill, abortion without medical indication and IVF are generally accepted practices. In all these practices embryos are created and sacrificed for purposes regarded as important and beneficial. Likewise, it is to be expected that if therapies were to be proven for serious illnesses, using hES cells, many people objecting to hES cell research now will not refuse such treatments when they or their loved ones are suffering or dying from a disease for which no other treatment is available. The same can be expected at the level of policy. Will societies that continue to ban or severely restrict hES cell research deny any such treatments to their citizens? This is very unlikely. Of course there will be some individuals who will refuse treatments based on embryo research or products derived from embryos. Just as there are people who, based on their deeply held beliefs, refuse euthanasia while suffering terribly from a terminally illness, and women who refuse to undergo abortion, which would save their own life, to protect the life of their foetus (like Gianna Molla who, while she was pregnant, was diagnosed with a large cyst in her womb, which required surgery and abortion of the fetus. She refused abortion and the child was born healthy, but Gianna died 7 days later. She is now regarded as the martyr and patroness of pro-life and anti-abortion movements).

Here we come to a second reason for designing this advance directive. In a democracy it is not the opinion of the majority *alone* that determines public policy and regulations, nor should minorities close all the options down for their fellow citizens. The core values in a democracy are freedom and tolerance. As pointed out before, it is to be expected that only a significant minority will actually bring their professed beliefs into practice. When such beliefs are so at odds with self interest and the public good, why would such a minority have the right to block all the options for their fellow citizens? There is no agreement about what moral status to accord to an embryo, and there never will be. Looking for consensus or complex compromises that satisfy neither of the moral positions requires considerable effort and slows down important life saving research. It is time to look for better ways of dealing with the vested interests and entrenched positions in hES cell research, and we should do this in accordance with democratic values, that is, whilst maintaining a maximum degree of choice for citizens.

Respect for minority views can be shown by not imposing choices on them which they consider ethically unacceptable. If people who accord very high value to embryos refuse to benefit from the results of hES cell research, they should have the possibility to do so. But tolerance should not go in one direction only. Options open to some citizens should not be constrained because of deeply held, often religiously based views of others. These minorities should also tolerate the views and wishes of all their fellow citizens who want to have their lives and the lives of their loved ones saved with treatments based on hES cell research or products derived from embryos. However, the problem goes beyond the issue of minority versus majority. Even if a majority in society would reject hES cell research because it 'kills' human embryos, this would not be a reason to block the research. Freedom of research is one of the most important rights and moral values in a democracy. It is not an absolute value and can be restrained by other important values such as the safety and respect for research participants and patients. However, in the context of hES cell research, the application of the principle depends greatly on the moral status of the embryo. A justification primarily based on a highly contested value is insufficient to restrict freedom of research to such a considerable extent.

3. WHICH WAY FORWARD?

The way forward in the stem cell debate and, accordingly, stem cell policymaking is to recognise that most people accord a *relative* moral status to the human embryo and are prepared to accept the creation and sacrifice of embryos for purposes considered as very important, such as life-saving therapies. Most people accord high value to embryos when these are included in a parental project, that is, when people create embryos to start a family, but in most cases (in IVF treatments), this value decreases when the family is completed and the embryos are 'left-over'. Those who do not share this viewpoint should, to the extent possible, have the choice not to benefit from hES cell therapies and they should have the freedom to defend their case, for example, by proving that there are equally effective alternatives that do not require the use of embryos. Stem cell therapies will surely be developed in the not too distant future. Focusing on one particular view on the moral status of embryos may crystallise both the issues and the sincerity of the participants in this crucial contemporary debate. We risk neglecting other issues that may be far more important to most citizens, including their safety and privacy, and their access to life-saving drugs and therapies. If we really do care about human lives, then we should not continue to be hostages of one particular viewpoint on the moral status of the embryo, but we should start to focus on these other issues. The proposed advance directive is meant to dramatise the consequences of consistently holding a particular moral view and to stimulate discussion about how the debate should proceed.

ACKNOWLEDGEMENTS

I want to express my gratitude to the Voluntary Euthanasia Society (VES) in the UK and especially to Deborah Annetts, who was so kind as to let me adapt their living will for the purpose of this paper. The VES have no responsibility whatsoever for the use I have made of it here. I wished, however, to use a standard and well accepted and well thought out format for advance directives, hence my choice of that developed by the VES. I am also grateful to John Harris for very helpful comments on an earlier draft.

CONCLUSION

Of right and wrong he taught Truths as refined as ever Athens heard;
And (strange to tell) he practis'd what he preach'd.

John Armstrong
The Art of Preserving Health. Book IV, Line 301.

1. INTRODUCTION

"Every truly effective technological advance is a challenge to culture, politics and ethics. This is as true for discoveries of fire, the wheel and gunpowder, as it is for the Atom bomb, space travel and biotechnology", said Edmund Pellegrino of the Georgetown University Medical Center and new Chair of the US President's Council on Bioethics.[1] Indeed, like many new technologies stem cell research raises several substantial ethical issues and creates a challenge for all societies. For example, as is the case with many new technologies, the promises of stem cell research need to be weighed up against the risks related to the research or the (inappropriate) application of the research. This precautionary approach, directed at preventing potential harm to people, has been the main reason for blocking the use of preimplantation HLA-typing to create a haematopoietic stem cell donor. In the case of hES cell research it is not, however, a precautionary approach that prevents or slows down the research, but primarily the fact that society is morally divided about whether or not human embryos can be sacrificed to obtain hES cells and the subsequent public policy response to this moral diversity. It is this policy response, in particular the compromise attempts and their moral grounds that became the primary focus of my dissertation.

2. MAIN CONCLUSIONS

I started my dissertation with the question as to what countries that ban hES cell research will do if effective treatments based on hES cell research were to be developed in other, more permissive countries or jurisdictions. There are three possible options: (1) maintaining their prohibitive policy, (2) allowing some hES cell research, albeit under severe restrictions, by adopting one of the compromise positions upon which most countries' hES cell policy is grounded, or (3) adopting a permissive policy that allows, under well-defined conditions, the creation and use of embryos for hES cell research.

Critical analysis of the moral grounds supporting these policy options led me to the conclusion that the moral grounds underlying policy option 2 are not sustainable; that the moral grounds for policy option 1 can only hold true if these countries also prohibit all other practices in which embryos are 'instrumentalised', as well as refuse to benefit from hES cell research; and that the moral grounds for option 3 are embedded in a strong moral theory, which makes it a valuable option as a moral basis of stem cell policy in pluralistic democratic societies. Four reasons underlie the claim that option 3 has strong ethical force:
(1) the compromises are not sustainable, (2) there is a moral imperative to conduct hES cell research, (3) the embryo is not treated as 'one of us' and (4) a policy that allows hES cell research is compatible with revealed beliefs of many people in society and with important democratic values. A review of the reasons:

2.1. The compromises are not sustainable

Critical analysis of the ethical arguments underlying the two main versions of the intermediate posi-

tion - the *use-derivation* and the *discarded-created distinction* - has shown that both compromises cannot be sustained and therefore cannot serve as a solid ethical basis for stem cell policy. The *use-derivation distinction* cannot be guaranteed in practice, and arguments making a moral difference between using spare IVF embryos and research embryos for stem cell research fail. Not only are both compromises based on insufficiently grounded arguments, it was also demonstrated that neither of the versions of the intermediate position, and their variants, succeed in their aim, viz: finding a 'happy medium' between the two polar positions on embryo research. The main reason is that the compromises are directed at the professed beliefs of their possible audiences and not at what may be their actual beliefs, as revealed through their acts/omissions and the practices they accept. A central claim in my dissertation has been that, given possible inconsistencies between revealed and professed beliefs, only by including revealed beliefs in our analysis can we assess the legitimacy of the compromises and their effectiveness in stem cell policymaking. Taking into consideration these revealed beliefs we cannot but conclude that the world seems to divide into two opposing groups. First, those who think the embryo should be protected at any price and who consequently, if they apply their professed beliefs consistently, should oppose any practice in which embryos are instrumentalised (such as IVF and embryo research). The other group holds the opinion that the embryo may deserve respect but lacks ultimate value and that the respect due to it can be weighed up against other important values (such as the need of people who seek genetically related children or the need of people who could be helped with treatments based on stem cell research). The latter group needs neither of the two compromises, as they already accept the instrumentalisation of embryos for important purposes. People who really believe the embryo is 'one of us' and merits the same protection as human persons cannot be satisfied by any one of the intermediate positions. They can only accept research that does not kill those who are 'one of us' or that does not benefit from killing those who are 'one of us'.

Indeed, the failure of the intermediate position to find a 'happy medium' has proven to be the case in many countries that have adopted a hES cell policy grounded on some version of the intermediate position. This failure has led to an increasing trend to find seemingly neutral scientific solutions in order to overcome the problem of killing embryos in the hES cell derivation process. I have discussed two such proposals and have argued that, just like the intermediate positions, they fail to take into account the revealed beliefs of their possible audiences and therefore become redundant compromises. The proposal to use 'organismically dead' embryos (the 'Landry-Zucker proposal') is a redundant compromise as it is meant for a group that already accepts IVF, and thus the creation and sacrifice of embryos for beneficial purposes. Creating 'ANTities' as a source of hES cells (the 'Hurlbut proposal') will not solve the problem of embryo killing either, as the proposal is directed at people who consider the embryo to be one of us, and who only accept stem cell sources with an unambiguous moral status, such as adult stem cells. I concluded that since the question of how to define an embryo and what constitutes its value involves a normative value judgment, it is very unlikely that science alone will solve the moral dilemma in hES cell research. (Unless stem cells with the same functional capacity as hES cells can be obtained from sources that have no significant moral status). What science can do,

however, is direct these normative value judgments and point out possible inconsistencies in according moral status to embryos and embryo-like entities. By reference to peer-reviewed publications, we demonstrated that hES cells and embryos exhibit the same inherent potential to become a person. Tetraploid technology raises the possibility that a *single* hES cell line could form all the extraembryonic and embryonic tissues required for successful formation of a human person. Therefore, where a hES cell line has been successfully derived and cryopreserved it is capable of forming a person on the condition that human intervention places it in the appropriate environment so that it can continue its development. This is no different from a cryopreserved embryo. Consequently, those who want full protection of embryos because of their inherent potential to form a person should give the same protection, and thus accord equivalent moral status, to hES cells. This finding has serious consequences for stem cell policies grounded on the use-derivation distinction, such as those of the US and Germany. After all, this distinction has been shown not to hold true on the basis of scientific evidence. We concluded that the inherent potential argument opposing hES cell research is flawed, or at least not sufficient to prohibit hES cell research without any further justification, as it can be used to both oppose and defend hES cell research. Consequently the argument is inadequate as a basis of stem cell policy.

Critical analysis of the compromises, either by adopting some intermediate position or by developing a seemingly neutral scientific solution, brought us to the conclusion that these compromises prevent or slow down hES cell research on the basis of a weak ethical argumentation, without reaching their aim of finding a way to resolve moral conflict in this field. This is only problematic, however, if we have a strong moral obligation to pursue hES cell research. This brings us to the second reason that underlies our main conclusion.

2.2. The moral imperative to conduct hES cell research

To consider the question as to whether or not the problem of restraining or blocking some types of stem cell research is overestimated, I investigated two possible applications of stem cell research in depth. I examined why they have caused controversy, and whether the moral justifications for prohibiting them can hold true. In both cases, I gave a consequentialist defence and departed from the view that an embryo has no significant moral status.

I first dealt with the possibility of using preimplantation HLA-typing to have a tissue matched child that can serve as a haematopoietic stem cell donor. Critical analysis of the major objections to this procedure led me to the conclusion that none of these objections provide strong enough reasons to block the research and its applications. On the contrary, the person-affecting reason (to save a sibling) for using the procedure is not a reason to forbid the practice, but constitutes a strong argument in favour of it. Furthermore, I have argued that because sometimes we have stronger emotional bonds to people unrelated to us than to family members, the procedure should also be offered to couples who decide to have a tissue matched baby that can save someone whom they love. I concluded that since there are no indications that donor children will be harmed, and we know that some people will be saved,

it would be *unethical* not to allow this procedure and not to further explore its potentialities.

Similar conclusions were drawn after discussing the issue of cloning for research and therapy. It was pointed out that each of the objections to cloning may have solutions in the future and that, in so far as these objections have force, they only have force against cloning for self-transplantation and not against cloning for developing cellular models of human disease. Cloning could be of great benefit to humanity, as it holds the potential to immeasurably increase scientific understanding of human development and disease, as well as to revolutionize the practice of transplantation medicine. This provides a strong prima facie case in favour not just of allowing research, but positively supporting it through permissive legislation and public funding.

In both the cases of preimplantation HLA-typing and cloning, there are of course reasons for precaution, but these must be carefully balanced against delay in developing life-saving treatments. Research and its applications should only be prevented if it harms people or exposes them to risks in a way disproportionate to the benefits derived from them. Neither of the discussed applications of stem cell research risks harming any person to such an extent. They only stand to benefit people, now and in the future. To continue to hold back the research and its applications is to be responsible for the deaths of many people who perished while the development or the application of treatments was delayed. It is unethical to let people die by denying them treatments (that is, after all, what happened in the Tuskegee study[2]). This applies to future as well as present treatments. In conclusion, the consequences of restricting or banning important research that has the potential to alleviate human suffering and to save many lives, such as stem cell research, are serious and needs strong justification. Such strong justification has not been provided for banning cloning research and the use of preimplantation HLA-typing for creating tissue matched stem cell donors.

In the last chapter I investigated whether strong enough justification for restricting hES cell research has been provided by countries that have justified their stem cell policy on the basis of one of the compromise positions. I studied the case of hES cell policy in the US, which is primarily justified by the avoidance of moral complicity in 'killing' human embryos. I concluded that current US stem cell policy severely restrains freedom of research and leads to a lack of federal oversight and consequently, a lack of protection of public health. Analysis of the moral grounds of US policy indicated that this restriction of freedom of research does not result from a precautionary approach that aims at the protection of patients or research participants, but greatly depends on one particular view on the moral status of the embryo, namely of those who think the embryo is one of us. I argued that current US policy cannot justly deny support to hES cell research, which holds great potential to improve and protect citizen's health, merely because one particular group in that society objects to it on the basis of a highly contested value. First, there is the political argument that in a democracy, it is untenable and undesirable to have a tax system in which taxpayers are allowed to choose to which government approved programs their money should go to. This certainly applies to important scientific research

programmes. Secondly, as pointed out before, preventing or restraining important research requires strong justification, grounded on evidence and solid arguments that originate from a general moral principle or theory. In the second part of the paper, I argued that the Government has not provided such a strong justification. Merely denying federal funding for hES cell research is actually pursuing a permissive policy. Through the Nazi analogy, I showed that those who oppose embryo killing can only be satisfied with Bush's federal funding restrictions if his policy would at the same time condemn and prohibit all embryo-killing in the US. (Indeed, pro-life movements in the US are calling upon the government to prohibit IVF, proclaiming, "IVF kills babies."[3]). I concluded that either President Bush does not really intend taking into account the views of the target group of his compromise - those who think the embryo is one of us - which destroys the ethical justification for his policy, or he does not really believe the embryo should get special protection. If the United States, through its government, is serious about its professed beliefs and the moral theory upon which it bases its policy, it should prohibit the continuing and uncontrolled killing of embryos on an industrial scale in the US. If it does not do so, then the moral compromise cannot stand the test of consistency and, consequently, cannot serve as a solid ethical basis for restrictive hES cell policy. It is surely, as we have shown, unethical to discourage potentially life-saving research by denying federal funding on the basis of a weak moral position. Moreover, current US stem cell policy makes the government not only morally complicit in the killing of embryos, but also in the deaths of people whose life could have been prolonged if the research and its applications would not have been delayed.

Again, we concluded that the intermediate position cannot be sustained because it is grounded on arguments that cannot stand the test of consistency and because it is not directed at people's revealed beliefs about embryo protection.

My 'advance directive to protect embryos' draws further upon the problem of inconsistencies between professed and revealed beliefs. Through this so called 'living will', those who believe the embryo should be protected at any price and who oppose hES cell research are offered the opportunity to commit themselves in advance to foregoing any benefit of hES cell research. If they are sincere about the arguments and principles they profess, such a course would be a fair choice. If they do not accept the advance directive now, how can their arguments be taken seriously and have any weight as a moral basis for stem cell policy? And if they, when their own hour of need arises, will not wish to renounce effective treatments developed through hES cell research, will Governments that ban hES cell research deny their people such treatments? Are they prepared to accept the responsibility for the consequences of denying their people life-saving treatments? Are they willing to pay a price that high to protect the embryo? Pressure of their citizens to have access to these therapies will grow. The debate that this will evoke will reveal what values people really find most important in life. This brings us to a third reason as to why the moral basis for a policy that allows hES cell research is embedded in a strong moral theory that makes it a valuable option for grounding stem cell policy on.

2.3. The embryo is not treated as 'one of us'

As noted before, it is very unlikely that anyone, with the exception of some radicals, in their own hour of need, will renounce the benefits derived from hES cell research. Even those who believe the embryo is one of us have shown in the past to accept the deliberate killing of embryos in exceptional circumstances (e.g. abortion). No society treats the embryo as 'one of us', or has ever done so. Most people seem to have respect and care for some kind of protection of the embryo, but these feelings can change and depend on people's intentions, more in particular whether or not the embryo is included in a parental project. They believe that, under certain conditions, embryos surplus to reproductive needs can be used for beneficial purposes (as I have argued, this can be extended to gametes). Consequently, a hES cell policy that allows the creation and use of embryos for hES cell research reflects the revealed beliefs on the moral status of the embryo of many people in society. Compromising on the moral status of embryos is impossible. Once one accepts certain uses of embryos it will always be hard to defend prohibitions of other uses for equivalent moral purposes. Does this imply a slippery slope to allowing any embryo research, without any limitations?

This need not be the case. Instrumentalisation of embryos may be acceptable, but from this it does not follow that embryos should be treated as mere objects without any value. Not because embryos *have* special value - this is a normative value judgment on which disagreement exists - but because there is a social advantage in treating the embryo with some respect. Many people have respect and care for some protection of the embryo. We have noted that there are forms of respect and deference which are less absolute and which admit of gradations. The respect one has for an entity does not exclude it, provided that a meaningful argument is presented, from being used as a resource for a goal which is believed to be important (I compared this with research on cadavers). A way to show respect to early embryos is by ensuring that they are used with care in research that incorporates substantive values such as the alleviation of human suffering (in accordance with the principles of beneficence, non-maleficence and proportionality), by guaranteeing that their potential will not be wasted (in accordance with the principle of waste avoidance) and that they will only be used if there are no less contentious means of achieving the intended goal (in accordance with the subsidiarity principle). Well regulated hES cell research can be consistent with these widely accepted principles. Of course, disagreement can still exist on the scope of these principles. However, arguments for establishing scope, such as stating that the protection of the embryos falls within the scope of the principles of non-maleficence, like the principles themselves, have to meet the standards of adequacy and validity required for arguments to hold true.[4] We have shown that no strong argumentation that meets these standards has been provided. First, most of those who claim the embryo is one of us do not apply their professed beliefs consistently. Second, views on the embryo as a person are mostly religious based. Religious views cannot form the basis of public policy in pluralistic democracies. Third, as we have argued, secular views that defend the absolute protection of the embryo because of its potentiality to become a person fail. Moreover, the validity of *not* considering the embryo as one of us is corroborated by scientific evidence and analysis of the (changing) characteristics of a human in development. This is where science has an important role to play in the hES cell debate. Some ideas about the embryo and what

constitutes its value are simply outdated in the sense that science has shown them to be erroneous or at least suspect. New technical possibilities to manipulate embryos and aggregate and disaggregate their cells will continuously challenge our views about the embryo and what constitutes its value. Even if these views cannot conclusively be shown to be fallacious, at least, they can be shown to be inconsistent. Moreover, the more developed these techniques and our scientific knowledge about the origin of life and human development will become, the more our terminology will need to be refined. This will clarify and facilitate the debate process, as current categories are not practical and are applied inconsistently.

2.4. A stem cell policy that allows hES cell research would be compatible with a morality widely accepted in many societies

A more liberal policy that would allow the creation and use of embryos for hES cell research under strict conditions would be compatible with revealed beliefs and with widely accepted principles of many people in society. Although this widely accepted morality is subject to continuous review and modification in the light of new evidence and better arguments, it provides us good reasons now to move away from the issue of the moral status of the embryo and concentrate on other issues, such as those related to the application of the research. Moral diversity on deeply held beliefs about the embryo must be respected. But, as John Harris has said, "powerful moral reasons to pursue research should not be drowned by the powerful reasons we have to respect people's fundamental views".[5] Respect for morally diverse views, does not require that we as a society prohibit or severely restrict hES cell research. Pursuing and supporting hES cell research, as we have shown, is in the interests of all people, now and in the future. As we have argued, the compromise attempts that restrict hES cell research cannot be sustained and therefore cannot offer a legitimate moral basis for stem cell policy. Moreover, advocates of these compromise positions often do not concede all the implications of their arguments, by which they risk sidestepping issues of equal or even greater moral importance, such as patients' safety and people's access to life-saving drugs and therapies.

It is time to look for other and more creative ways to deal with the vested interests and entrenched positions in hES cell research and we should do this not only in line with revealed beliefs of many people in society, but also in accordance with democratic values, such as freedom and tolerance. Respect for people's fundamental beliefs on the embryo can be shown by not imposing on them choices which they consider unacceptable. If people who accord absolute value to the embryo, do not wish to benefit for hES cell research, they should have the opportunity to do so (for example, stem cells and stem cell lines should be identified with respect to their origin. Patients as well as researchers who feel ethically uncomfortable with the use of certain types of stem cell could then avoid participation in the use of these stem cells). But, as I have argued, tolerance should not go in one direction only. Options that are of great interest to present and future generations should not be constrained because of deeply held, often religiously based but highly contested views of others.

Concerns for ethical issues and respect for people's revealed beliefs, however, provide reasons for oversight and regulation. As pointed out, strategies that can promote community acceptance and cohesiveness, include transparency of research, public control and predictability, legislative control, independent oversight, continuous review, public participation and respect for value diversity and reassurance and demonstration of benefits of the research. A global stem cell project with central coordination and international collaboration, and a framework that addresses scientific, medical, ethical and social concerns could really address and answer people's ethical concerns.

3. Quo Vadis?

The way we respond to practical dilemmas can differ from our professed beliefs about abstract problems. These revealed beliefs should influence our ideas about what is good or bad. They say something about the morality we accept. (Many practices that are now routine and uncontroversial, such as blood transfusion and organ transplantation, were once considered unethical by many). This morality should be projected onto the principles we profess. If our reactions in real-life situations are inconsistent with the beliefs we profess, then these principles and/or their scope may have to be reviewed and modified in the light of the morality we accept or wish to retain. It is important to realise that there is a two-way interaction between the principles we accept and our practices. There is nothing fundamentally wrong with temporal inconsistency, as it is part of moral development. There is something seriously wrong, however, with knowingly being inconsistent. Just like we cannot force people to act morally, we cannot force them to apply their principles consistently. What we can do, however, is point out inconsistencies by critical analysis of the arguments and by properly informing people through an honest and open debate. Justifying stem cell policy by reference to a moral position that is not based on solid arguments and on the basis of principles that are not applied consistently in practice, is not only hypocritical, but also, in a sense, instrumentalises ethics in order to find a purely political compromise.

I call for an open debate in which the arguments and their grounds are clearly stated and tested in all sorts of ways and in which people are informed. This is the only way to achieve moral development and hopefully moral progress. Rather than developing moral compromise, a more likely way to achieve broad consensus is to identify and clarify our revealed beliefs, place them in a broader context of already accepted moralities, and stimulate critical reflection and debate. I hope that through this dissertation I have contributed to this aim.

As Ruth Faden and John Gearhart have stated: "Hype and symbols will not advance our [national] debate about stem cell research. Facts and frankness will. So let's be frank".[6]

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GLOSSARY

Adult stem cells: stem cells found in the organism after birth that replenish tissues in which cells often have limited life spans. They are more differentiated than embryonic stem cells or embryonic germ cells.
Allele: an alternative form of a gene. One of the different forms of a gene that can exist at a single locus (spot on a chromosome). Also one of the different forms of any segment of a chromosome.
Allogeneic transplantation: cell, tissue or organ transplants from one member of a species to a genetically different member of the same species.
Altered nuclear transfer: a proposed method, using a modified form of somatic cell nuclear transfer (SCNT), of producing a biological artefact from which human pluripotent stem cells could be derived.
Anaemia: a condition of the blood where red blood cells are in some way not operating to their required optimum level.
ANTities: embryo-like entities generated through altered nuclear transfer (ANT)
ART (assisted reproduction techniques): medical treatments or procedures which involve handling human eggs and sperm for the purpose of inducing a pregnancy.
Autologous transplantation: cell, tissue or organ transplants from one individual back to the same individual. Such transplants do not induce an immune response and are not rejected.
Auto-immune diseases: diseases in which antibodies made by the body destroy its own cells.

ß-cells: insulin secreting cell type of the pancreas.
Biological artifact: an artificially created non-embryonic but embryo-like cellular system, engineered to lack the essential elements of embryogenesis but still capable of some cell division and growth.
Blastocoel: the fluid filled cavity within the blastocyst.
Blastocyst: a mammalian embryo that comprises an inner cell mass and the outer layer of trophoblast cells sealed together to maintain blastocoel. This stage is normally reached 5 to 7 days after fertilisation; the stage at which the implantation process in the uterus begins and the embryo consists 50-150 cells.
Blastomeres: cells into which a fertilized egg divides during cleavage stage.
Blastomere extraction: removal of one or two blastomeres from the embryo *in vitro* at about the 8-cell stage, usually in order to perform preimplantation genetic diagnosis and screening.
Blastula: an early stage of embryonic development (roughly 100-200 cells) at which the cells of the morula are rearranged to form a hollow sphere; at this stage of embryonic development in humans and other mammals, the embryo is generally called a blastocyst.
Bone marrow: the soft, loving tissue that fills most bone cavities and contains haematopoietic stem cells and mesenchymal stem cells.

Cardiomyocyte: the precursor to heart muscle cells.
Cell nuclear transfer: cloning technique where the nucleus of a cell from the organism is transferred into an oocyte whose own nucleus has been removed.
Cell-differentiation: the progressive restriction in potential cell fates, until acquisition of a specialised function is achieved.

Chimaera: an organism composed of cells derived from at least two genetically different cell types. The cells could be from the same or separate species.
Cleavage arrest: spontaneous cessation of cell division in an early embryo.
Clonal expansion: one cell giving rise to millions of identical cells.
Clone: an organism that has an (or nearly) identical genome to that of another organism.
Cloned embryo: an embryo arising from the somatic cell nuclear transfer process.
Compatibility: immunological characteristic of cells or tissues allowing them to be tolerated by other cells or tissues. It enables tissues to be grafted to others effectively.
Culture medium: the broth that covers cells in a culture dish, which contains nutrients to feed the cells as well as other growth factors which may be added to direct desired changes in the cells.
Cryopreservation: the protective storage, usually in liquid nitrogen at - 196°C, of cells, gametes, embryos and women's eggs.
Cystic Fibrosis: a disorder of the mucus-secreting glands of the lungs, the pancreas, the mouth, and the gastro intestinal tract.
Cytoplasm: the contents of a cell, other than its nucleus. It contains mitochondrial DNA.

Dedifferentiation: a procedure whereby differentiated, somatic cells are restored to a more undifferentiated, multipotent condition.
Diamond blackfan anaemia (DBA): a blood condition, characterized by an inability to produce red blood cells, caused by a failure within the bone marrow.
Differentiation: development of an unspecialised cell, without any function, to a cell with a specific function, such as a blood cell, a nerve cell, etc.
Diploid: refers to the full complement of chromosomes in a somatic cell, distinct for each species (46 in human beings).
Directed differentiation: manipulating stem cell culture conditions to induce differentiation into a particular cell type.
DNA: deoxyribonucleic acid, a chemical found primarily in the nucleus of cells. DNA carries the instructions for making all the structures and materials the body needs to function.
Dopamine: one of the key transmitter substances which passes between nerve cells.

Ectoderm: upper, outermost layer of a group of cells derived from the inner cell mass of the blastocyst; it gives rise to skin nerves and brain.
Egg: ovum or oocyte; the mature reproductive cell.
Embryogenesis: process whereby the embryo develops.
Embryonic germ (EG) cells: undifferentiated stem cells derived from the gonadal ridge of a 5-11 week old fetus. In mammals, they are the in vitro counterpart of primordial germ cells which eventually give rise to gametes.
Embryonic stem cells: undifferentiated cells derived from the inner cell mass of the blastocyst that have the potential to proliferate indefinitely and differentiate into many different tissue types.

Embryonic stem cell line: populations of dividing cells established from ES cells obtained from a single embryo, cultured under *in vitro* conditions that allow proliferation without differentiation for months to years.
Endoderm: innermost of the three primary layers of the embryo; origin of the digestive tract, liver, pancreas, urinary bladder and lining of the lungs.
Endothelial cells: cells from the endothelium, the thin layer of cells that lines blood and lymph vessels.
Enucleated egg: an egg from which the nucleus has been removed.
Epiblast: the outer layer of a blastula that gives rise to the ectoderm after gastrulation.

Fanconi anemia: a rare inherited form of aplastic anaemia in which the bone marrow fails to produce blood cells normally.
Feeder layer: cells used in co-culture to maintain pluripotent stem cells.
Fertilisation: begins when the male gamete penetrates the oocyte and ends when female and male chromosomes come together to form the zygote.
Fibroblast: progenitor cell that forms a part of connective tissue, capable of forming collagen fibres.
Follicle stimulating hormone (FSH): a hormone secreted by the anterior pituitary that promotes gamete formation in both males and females.
Functional genomics: the study of gene functions and their interrelationships. A genome sequence by itself doesn't describe the function of genes, only their structure.

Gamete: an egg or a sperm, or a cell that can become an egg or a sperm. Not classified as a somatic cell.
Gene: the unit of inheritance; that element of DNA in which the amino acid sequence of a protein is encoded. Everyone inherits two copies of each gene.
Gene therapy: a clinical technique of introducing genes or DNA into patient's cells.
Genome: the complete genetic code of an organism.
Germ cells: general term for sperm and eggs and their precursor cells.
Germ layers: the three primary tissue layers arising in the embryo - endoderm, mesoderm and ectoderm - from which all other somatic tissues develop.
Gonadal ridge: an elevated portion of the developing embryo that contains the primordial germ cells.
Graft-versus-host disease: condition that occurs following transplantation in which the donor's immune cells make antibodies against the host's tissues.

Haematopoietic: blood-forming
Haematopoietic stem cells: early precursor cells giving rise to all cells in the blood and lymphatic organs.
Hepatic: related to the liver.
Hepatocytes: liver cells.
Heterologous: refers to a transplant from an unmatched donor.

HLA: human leukocyte antigen - the main factor in tissue matching for organ transplantation.
HLA-typing: a method of distinguishing cells to determine if the donor's immune system is compatible with that of a potential recipient.
Homologous recombination: recombining of two like DNA molecules, a process by which gene targeting produces a mutation in a specific gene.
Huntington's disease: a late but variable age onset lethal human disease of nerve degeneration. Inherited as an autosomal dominant phenotype.
Hybrid: an individual produced by the crossing of two different strains or sometimes species.

Immunodeficient: lacking immunity and so susceptible to infection.
Immunosuppressive: suppressing a natural immune response.
Implantation: the process of trophoblast attachment and outgrowth into the lining of the uterus.
Imprinting: a modification to a gene that occurs in the ovary or the testis and influences what cells can express the gene without altering the base sequence of the gene.
Inner cell mass: the cluster of cells inside the blastocyst that give rise to all embryonic and some extraembryonic tissue.
IVF embryo: an embryo produced by in vitro fertilization.
In vitro: Latin for, 'in glass'; in a laboratory dish or test tube; an artificial environment.
In vitro fertilization: an assisted reproduction technique in which fertilization is accomplished outside the body.
In vivo: Latin for, 'in life', refers to processes taking place within a living organism.

Karyotype: chromosome characteristics of an individual cell or cell line, the microscopic appearance of a set of chromosomes, including their number, shape, and size.
Knock-out mice: mice produced by different methods of genetic manipulation which result in the elimination of a specific gene.

Lineage: the descendants of a common ancestor

Major histocompatibility complex: mouse equivalent of HLA.
Meiosis: the process by which a diploid cell nucleus divides into four nuclei each with half the number of chromosomes of the parent nucleus.
Mesentery: responsible for connecting the small intestines to the back-wall.
Mesoderm: middle layer of a group of cells derived from the inner cell mass of the blastocyst; it gives rise to bone, muscle, and connective tissue.
Mesenchymal stem cells: cells from the immature embryonic connective tissue, which produce bone, cartilage, fat and muscle.
Mesoderm: the middle of the three primitive germ layers of the embryo. Mesodermal cells give rise to most of the cardiovascular system, blood cells and bone marrow, the skeleton, smooth and striated

muscles, and parts of the reproductive and excretory systems.
Mitochondria: organelles in the cytoplasma of a cell. They provide the energy for the cellular processes including that of meiosis. They have their own genetic disposition.
Monozygotic: derived from one zygote.
Morula: A cleaving egg consisting of approximately 12 compact blastomeres, surrounded by the zona pellucida (days 3-4 after fertilisation). Some thought this stage resembled a mulberry and, therefore, it is called a morula (Latin, Mulberry).
Mouse embryonic fibroblast: cells used as feeder cells in culturing pluripotent stem cells.
Mutliple sclerosis: degenerative neurological disease, characterised by degradation of the white matter of the nervous system.
Multipotent: capacity to give rise to some adult cell types.
Multipotent adult progenitor cells (MAPCs): cells isolated from bone marrow that can be differentiated into cells with characteristics of cartilage, fat, and bone.

Neonatal stem cells: stem cells from the umbilical cord blood.
Neurodegenerative disease: a disorder caused by the deterioration of certain nerve cells (neurons). Changes in these cells cause them to function abnormally, eventually bringing about their death. The diseases, Alzheimer's, Parkinson's, and Creutzfeldt-Jacob, as well as multiple sclerosis, are due to neuronal degeneration in the central nervous system.
Nuclear reprogramming: the process of changing gene expression from a differentiated cell. state to an undifferentiated cell state to restore pluripotency.
Nuclear transfer: replacing the nucleus of one cell with the nucleus of another.
Myocardium: heart muscle.

Organismic death (of an embryo)-concept and **criterion:** as proposed by Landry and Zucker, the concept of organismic death for an early-stage human embryo is defined by irreversible loss of "the capacity for continued and integrated cellular division, growth, and differentiation"; their proposed criterion for determining organismic death is "irreversible cessation of cell division in the embryo observed in vitro."
Oocyte: a female germ cell in the process of development. A cell that gives rise to an ovum by two meiotic divisions. Primary oocytes are diploid and undergo meiosis to give secondary oocytes which are haploid, and meisois of a secondary oocyte produces an ovum (egg).
Ovasome: a new term proposed to describe egg activation for the purpose of creating stem cells rather than an embryo.

Parthenote: a cleaving egg that has been activated to initiate cell division without being fertilized by sperm.
Pharmacogenetics: pharmaceutical treatment that is tailored to the individual, with regard to genetic criteria - for example, by choice of drug or dosage.

Plasticity: ability of one type of stem cell to undergo a transition to cells from other lineages.
Pluripotent: : capacity to differentiate into some extraembryonic and all embryonic and adult cell types.
Polar body biopsy: removal of the polar body in order to determine the genetics of the oocyte.
Precursor cells: see progenitor cells
Preimplantation genetic diagnosis: use of genetic testing on a live embryo to determine the presence, absence or change in a particular gene or chromosome prior to implantation of the embryo.
Primary germ layers: the three initial embryonic germ layers - endoderm, mesoderm, and ectoderm - from which all other somatic tissue types develop.
Primitive streak: the depression in the ectodermal layer of the embryonic disc caused by mesodermal cells.
Primordial germ cells: the progenitors of sperm and eggs.
Progenitor cells (or precursor cells): an early descendant of a stem cell. Division of progenitor cells always results in two specialised cells, and not in other progenitor cells (they cannot self-renew). They can only give rise to a limited number of cell-types.
Proliferation: rapid reproduction of tissue.
Pronucleus stage: state of oocytes after penetration of the sperm, but before resolving of the nuclear membrane.

Regeneration: the replacement of diseased or damaged parts of a body with new parts, for example, cells, tissues, or organs.
Research embryos: embryos created solely for the purpose of research.

Somatic: all cells and tissues of an organism with the exception of sperm and eggs and their precursor cells, termed germ cells.
Spermatocyte: diploid germ cell which will undergo two meiotic divisions to give haploid spermatids.
Stem cell: an undifferentiated cell with the capacity for unlimited or prolonged self-renewal and the capacity to produce at least one type of highly differentiated or specialised cell.
Stem cell line: Stem cells which have been cultured under in vitro conditions that allow proliferation without differentiation for months to years.
Stem cell niche: a restricted locale in an organ that supports the self-renewing division of stem cells and so prevents them from differentiating.
Stem cell research: the study of stem cells, either *in vitro* or *in vivo*.
Superovulation: the medical stimulation of the ovary with the hormones to induce the production of multiple egg containing follicles in a single menstrual cycle.

T-cell: any of the lymphocytes that mature in the thymus and have the ability to recognize specific peptide antigens through the receptors on their cell surface.
Teratoma: non-malignant tumour consisting of different types of tissue, as of skin, hair, and muscle,

caused by the development of independent germ cells.
Teratocarcinoma: germ cell tumour (usually of the testis).
Therapeutic cloning: isolation of ES cells from embryos produced by nuclear technologies. Cell products derived from those cells are genetically identical to the donor of the nucleus and are not immunologically rejected after transplantation into this person.
Totipotent: capacity to differentiate into all extraembryonic, embryonic and adult cell types.
Transdifferentiation: the capacity of somatic stem cells to give rise to cell types of other lineages to which they do not normally give rise to in the body.
Trophoblast: the extraembryonic tissue responsible for implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.

Undifferentiated: not having changed to become a specialized or fully differentiated cell type.
Uterine transfer: transfer of an IVF embryo to a woman's uterus with a view to implantation and gestation.

Xenotransplantation: transplantation of viable cells or tissues from one species to another.

Zygote: the final stage of fertilisation, the single cell formed when the two sets of chromosomes, one from the male and the other from the female gamete, have joined.

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EDUCATION

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2004-2005: Project consultant for CLEMIT: Developing an operational ethical framework to analyse and monitor the ethics of creating and redesigning human beings. Research project funded by the European Commission, Science and Society.

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Work done: Literature survey on cloning
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- Devolder K. What's in a name: Entities, embryos and ANTities in the stem cell debate.
- Devolder K., Harris, J. Compromise and Moral Complicity in the Embryonic Stem Cell Debate.
- Devolder K., Romeo-Cassabona C., *et al.* Cloning for reproduction and therapy: where to draw the line in ethics and law?
- Analysis of Discussion of Council of Europe on Article 18 in the Convention of Biomedicine 1997.

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PRIZES

2003: 1st prize poster presentation. First Doctorandi Colloquium. Faculty of Arts and Philosophy, Ghent University.

PUBLICATIONS

Books

Devolder K., Braeckman J. *Copyright. Een bio-ethisch essay*. Leuven: Leuven University Press, 2001.

Summary: The authors of *Copyright* argue that there is a need for an educated debate on human cloning that is held without evoking panic, but also without arousing exaggerated expectations. They first provide an overview of the most contemporary biotechnological developments. Using many examples, the authors explain how biotechnology can be approached from an ethical perspective. They then focus on the discussion that emerged after the birth of Dolly, the first mammal that came about through somatic cell nuclear transplantation. Devolder and Braeckman focus on the question of whether 'human cloning' is ethically acceptable. In contrast to many other authors, their answer is not categorically critical. They analyse and discuss the main counterarguments using data from various scientific disciplines. These counterarguments include problems surrounding personal identity, human autonomy and dignity, the question of what is natural and unnatural, the difference between planned and coincidental reproduction, etc. The authors also discuss at length the cultural and historical aspects that give rise to the debate about cloning. The conclusion of their analysis is that there is currently only one legitimate argument for banning human reproductive cloning, namely that the technology is not fully developed yet and is therefore too risky to be applied to humans. Perhaps this will be solved at some point in the future. Should this become the case, cloning, then, might offer possible solutions for a number of human problems especially with regard to infertility. The authors do not shy away from controversial issues in their analysis of the pro and counterarguments. They address the problems of eugenics, so-called therapeutic cloning, research on embryos, and other issues. The book offers a sampling of the most important bioethical debates and takes a clear stand on the most-often discussed scientific and technological breakthroughs of the last several decades.

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Devolder K., Harris J. Compromise and Moral Complicity in the Embryonic Stem Cell Debate. In: Athanassoulis, N, ed. *Philosophical Reflections on Medical Ethics*. Palgrave McMillan: 88-108, in press.

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Book reviews

Devolder K. Book review of Wilmut, I., Campbell, K and Tudge, C. The Second Creation, The Age of Biological Control. *Ethiek & Maatschappij* 2000; 3:76-8.

Contributions in newspapers and national journals

Devolder K., Braeckman J. La nouvelle eugénétique. *L'Agenda Gynécologie* 2001; 25:3-5.

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Seminars

Ethical aspects of stem cell research. 11 Feb 2003. Faculty of Arts and Philosophy. Ghent University.

Bioethics and stem cell research. 18 Feb 2003. Faculty of Arts and Philosophy. Ghent University.

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Cloning and stem cell research. 26 Nov 2003. Faculty of Bioscience Engineering. Ghent University.

Cloning for research and therapy. 17 March 2004. Faculty of Applied Economics. University of Antwerp.

The discarded-created distinction in the human embryonic stem cell debate. 10 March 2004. CSEP Senior Seminar Series. The Centre for Social Ethics and Policy. The University of Manchester, UK.

Stem cell research: the way to eternal life? 5 Nov 2004. Post-academic learning. Ghent University.

Ethics of cloning and stem cell research. 2 Dec 2004. Faculty of Bioscience Engineering. Ghent University.

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