HUMAN STEM CELLS
SOURCE OF HOPE AND OF CONTROVERSY

A study of the ethics of human stem cell research and the patenting of related inventions

Henk Jochemsen, PhD
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With contributions of

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This report is produced by the Prof.dr. G. A. Lindeboom Institute, Centre for Medical Ethics, Ede, The Netherlands and the Business Ethics Center of Jerusalem, Israel.

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CONTENTS

PREFACE

We live in a time of quick technological advances and an economic system in which large amounts of money are constantly seeking maximum return of investments, where ever in the world. Technology and economic growth have produced great benefits for many people even though they are not yet reaching a large proportion of the world population. Biotechnology both in medicine and agriculture probably is the prime example of the combination of science based technology and economic interests. However, the promise of certain types of benefits for groups of people and the expectations of a high return of investments make those who bear responsibility in organisations and institutions involved in the field forget that in these developments other values and interests are at stake.

The Prof. dr. G.A. Lindeboom Institute and the Business Ethics Center of Jerusalem see it as their mission to evaluate biomedical and economic developments with an international impact also from an ethical perspective. To remind ourselves, our societies and governments that an increase in scientific knowledge, technological advancements and economic growth are not the only values that matter to further a humane society though of course they may contribute to that if properly regulated. That is why we undertook this study on one specific area in the wider development just mentioned.

Since the field is clearly international, one of the institutes is based in a member state of the EU and political regulations in European countries are heavily influenced by the policy decisions at the level of the EU, this report and its recommendations are primarily directed at European politicians. But because the developments in Europe are affected by what happened in the USA we also have included a chapter on the situation in that nation especially with respect to patents on human cells and tissues. Furthermore, the main lines of the contents of this report have been discussed with organisations in the USA that are moved by similar concerns as the centres that produced this report in the first place. This is the reason why those organisations are endorsing this publication as a significant contribution to the debates that run on these issues at both sides of the Atlantic.

We thank dr. Elisa Garcia, dr. Asher Meir, dr. Ron Harris and dr. Henk Jochemsen for their good work on this manuscript, dr. Henk Jochemsen, who was involved in this project both as the director of the Prof. Lindeboom Institute and the holder of the Lindeboom chair for medical ethics at the Free University medical centre, Amsterdam, for leading the project and editing the report. Each author is responsible for her or his own text and not necessarily agrees completely with everything written elsewhere in the report.

We are very grateful to the Noaber Foundation for a grant that enabled us to carry out this project.

The help of dr. C.B. Mitchell, mrs. P. Kamphuis-Helsloot, MA, of mrs. M. den Hartog en mrs. N.A. de Ridder-Sneep, MA in research and in preparing the manuscript is gratefully acknowledged.

We hope this publication may contribute to an international decision making on human (embryonic) stem cell research and on patenting of related inventions that will support a just and humane society.

Prof. dr J.W Oosterhuis, chairman of the Prof.dr. G.A. Lindeboom Institute

Dr. P. Rosenstein, director Business Ethics Center of Jerusalem

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Introduction and recommendations

1 Background

Since 1998, when human pluripotent stem cells were first isolated, research on stem cells has received much public attention, both because of its extraordinary promise and because of relevant legal and ethical issues.

Put simply, stem cells are self renewing, unspecialised cells that can give rise to multiple types all of specialised cells of the body. Because many diseases result from the degeneration or death of a single cell type the introduction of healthy cells of this type into a patient may restore lost or compromised function. The science of stem cells has, during the last couple of years, already has led to unprecedented advances in knowledge of this class of cells. It is hoped that stem cells will become the best or even only possibility to retain health for people who suffer from serious debilitating conditions or devastating diseases such as heart diseases, diabetes, cancer and diseases of the nervous system such as Parkinson and Alzheimer. In addition the recently techniques that have been developed for the in vitro culture of stem cells provide unprecedented opportunities for studying and understanding key processes of human genetics and developmental biology. As a result scientists can now carry out experiments aimed at determining the mechanism underlying the conversion of the fertilised egg cell, a single undifferentiated cell, into the different cells comprising the organs and tissues of the human body. Although it is impossible to predict the outcomes human stem cell research contributes to our understanding of fundamental human biology that will likely hold remarkable potential for therapies and cures. With words of David Korn, M.D. AAMC's senior VP for Biomedical and Health Sciences Research we can say that "they are one of the grails that science has been trying to get its hands on for a long time. They offer a vision of an entirely new kind of therapy-cell replacement, which would transform the management and prognosis of diseases that are now not reversible and only poorly manageable"[1].

Although stem cells can be obtained from some organs of the body of adults - like skin, bone marrow, umbilical cord and foetal tissue- the immediate available source is formed by the 'surplus embryos' of in vitro fertilisation (IVF) treatments and the gonadal tissue of aborted foetuses. For years, supporters of embryonic stem cell research have claimed that only stem cells derived from embryos have the capacity to differentiate into any of the human body' s cell types and offer the potential for the full range of cures that scientists hope to develop with this research. Embryonic stem cells are valuable scientifically because they appear to combine properties not found together in other cell lines: they are easier to isolate, they like to be more plastic than other stem cells and they replicate indefinitely without undergoing senescence. For the removal of stem cells from frozen surplus embryos from in vitro fertilisation (IVF) procedures in fertility clinics, these embryo's are thawed and cultured in vitro. Subsequently, cells of the inner cell mass of the embryo is are extracted and cultured. The embryo is killed in the process. Derivation of stem cells from early human embryos and germinal stem cells from aborted, foetal tissues raise ethical, religious and policy concerns. Furthermore, the potential uses of stem cells for generating human tissues and perhaps organs is a subject of ongoing public debate. The ability of the cells to maintain their pluripotent

1 NIH prepares to fund stem cell research as Medical Community weighs in. AAMC Reporter april 1999; 8 (n 7).

character even after 4 to 5 months of culturing was demonstrated. But scientists are only beginning to understand their basic biology. They do not presume to know all the answers and real therapeutic possibilities of embryonic stem cell research. There is concern that these cells could also undergo a benign hyperproliferation, leading to cancerous growth.

Adult stem cells were considerate to be of less medical interest because they seemed to differentiate into a narrower range of cell types and because the production of large numbers of these cells is much more difficult than for ES. In 1999 unprecedented advances have been made in isolating and culturing pluripotent or maybe even totipotent adult stem cells that can either be used to regenerate a specific organ or to generate many different types of tissue.[2] [3] These findings are further described in Chapter 1. These breakthroughs have dramatically altered the field and render it quite possible that treatment of neural diseases such as Parkinson's and Alzheimer's as well as spinal cordon injuries, will not depend on destructive embryo research. With each passing month, research with these stem cells is revealing the huge potential of this area. In many areas even the most successful, embryonic stem cell research is eclipsed by results with adult stem cells in research that is promising therapies for patients. It is also important to note that, at this time, only adult human stem cells are understood well enough to have them differentiate reliably into specific tissue types, and have proceeded to clinical trials.

Behind the scientific and ethical controversies connected to stem cell research lurks another issue that, though not always openly, fuels those controversies. This is the issue of the patenting of inventions involving stem cells and its impact on the research and development of therapies and on the commercialisation and commodification of human body (parts). Patents -a traditional industrial policy tool to encourage private funding of research- pose new problems when they apply to human biological material. The indicated advances in research on human stem cells have also increased the importance of a reflection on the matter of patent protection of therapeutic methods -which have consistently been held non-patentable subject matter- and the patentability of human material, such as modified stem cell or tissues cultivated from these cells.

2 Scope of this report

Since stem cell research seems to be one of the most promising and controversial technological breakthrough of our time, it requires a well founded study of the really therapeutical possibilities of these cells and of the moral acceptability of the different sources of stem cells, particularly the use and production of embryos destined to experimental and therapeutic purposes.

2 Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, J Moorman M, Simonetti D, Craig S, Mrshak, DR. Multilineage Potential of Mesenchymal Stem Cells. Science 1999; 284: 143-7.

3 Works of Department of Neurosurgery and Stem Cell Institute at the University of Minnesota/ Altman Greg, Tufts University in Massachusetts.

The scope of this report is to conduct a study in order to propose recommendations for regulating stem cell research and to inform public opinion of the real current state of human stem cell research and its ethical implications. We aim to answer two major questions:

What are the ethical issues that are related to human stem cells research, and under what conditions will such research be ethically acceptable. A sub question of this topic is the question whether from a scientific medical perspective the use of embryonic stem cells is really necessary.

A second question that we aim to analyse in this report are the concerns associated with the patenting of stem cells and its impact on the development of the research and development of therapies. This in view of the fact that a large part of the research is conducted by private companies that seek a financial return of investment by the use of IPR.

This study will involve five more chapters dealing with the following topics: Ch. 2) a literature study of the real therapeutic possibilities of stem cells from different sources; Ch. 3) an examination of the ethical issues associated with research and the use of human (embryonic) stem cells; Ch. 4) an examination of the economic and ethical issues associated with the patenting and commercialisation of the stem cells; Ch. 5) a description of the present patenting regime in the USA and its problems when it comes to biomedical findings.

On the basis of these chapters we have formulated some main recommendations for policy with respect to research on human (embryonic) stem cells and related patents. These recommendations are presented below.

3 Main recommendations for public policy

The constant advancements in the field of adult stem cell research raise justified expectations that they will contribute significantly to treatments to patients with many kinds of diseases.

> *We recommend a strong stimulation of this kind of research. (Chapters 2 and 3).*

We consider the human embryo to be a form of human life, in fact the human being and therefore, on the basis of the Helsinki decoration, reject a full instrumental use of human embryos in research. This applies to so called spare embryos but also for embryos somehow created to serve as research material. Even if one does not consider the human embryo to be a human being there are prudential reasons to reject its fully instrumental use in research: a diminishing respect and protection of the most vulnerable forms of human life in society. Furthermore for the development of medical treatments embryonic stem cells seem to be less promising then adult stem cells.

> *So we would recommend national governments to prohibit or at least restrain the instrumental use of human embryos in research.*

> *At the European level we recommend on the basis of the principle of subsidiarity and the precautionary principle that no European funds be available for research that involves the deliberate destruction of human embryos. (Chapter 3)*

An ethical patent regime should encourage research which fulfils the promise of relieving suffering, discourage irresponsible treatment of research subjects, and also make a positive and humane statement about the place of medical research in our society. From our analysis we conclude in this area is that current patent law is well-equipped to encourage productive research, as long as the law is carefully applied and patents are given only to truly patentable inventions whose extent is clearly defined.

> *This leads us to recommend appropriate regulatory restrictions on sources and uses of stem cells in order to convey that IP owners do not have 'carte blanche'; they have a valuable commercial right but do not 'own' the basic building blocks of the human organism. For the same reason we favour process over product patents – this avoids a blunt statement regarding ownership of humanity. (Chapter 4)*

The special situation of human embryonic (stem and germ) cells in our view requires a special provision. Since embryonic cells are obtained from embryo's or foetuses and can lead to the production of gametes that by fertilisation can generate a new human being, patents on such cells or procedures by which they can be obtained, have a bearing on the human being itself.

> *We think that human beings should not be treated as patentable matter and recommend that patents that embrace human beings should be excluded in the patent laws. A detailed analysis of this issue and public debate should lead to a further clarification of the limits of patentable inventions. (Chapter 5).*

2

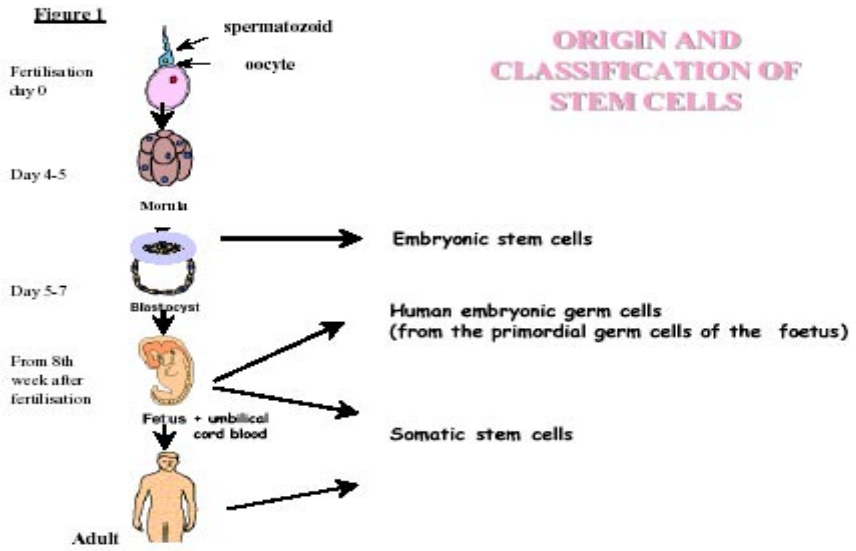
The science of stem cells

Dr Elisa Garcia and Dr Henk Jochemsen

1 INTRODUCTION

1.1. What are stem cells?

For many years it has been known that most tissues and organs of the human body have the ability to repair damage consisting in the destruction of cells caused by external (wounds, bruises) or internal factors (degenerative diseases). Apparently, those tissues contain cells that have retained the capacity to divide and differentiate into the cell types of damaged tissue. Those cells are called stem cells (see Figure 1).[4]



Stem cells are unspecialised cells that have the unique capacity for self-renewal and are capable of forming a least one, and some times many, of the different cell types that make up the organism. Stem cells are present at all stages of development and probably exist in all multi-cellular organisms, but their capacity to proliferate and differentiate into almost all of the specialised cells of the body appears to decrease in the course of the life of an individual. The degree of specialisation, in other words, increases with the years. Thus, we can talk of a stem cell's hierarchy according to a scale of specialisation. Some cells are able to give rise to an entire, normal, healthy organism. These cells are called totipotent, and the fertilised egg is the most obvious example. During the blastocyst stage, the cells of the organism begin to loose the

4 Taken from: Commission staff working paper. Report on human embryonic stem cell research. Brussels 3.4.2003, SEC (2003)441, p. 17

capacity to give rise to a whole new organism by themselves. However, they do maintain for some time the potential to develop into all or many of the more than 200 different cell types of which the organism will ultimately consist. This kind of stem cell is called pluripotent in stead of totipotent. In later developmental stages following gastrulation, these stem cells undergo further specialisation into stem cells that are committed under certain conditions to give rise to cells with a particular function. Such more specialised stem cells are called multipotent (or unipotent) and are present in many types of tissues of adult animals where they play an important role in tissue repair and homeostasis. So, until recently it was thought that only embryonic tissue contained pluripotent stem cells. At present, three types of mammalian pluripotent stem cell lines have been isolated: (1) embryonal carcinoma cells (EC) derived from testicular tumours called teratocarcinomas; (2) embryonic stem cells (ES) isolated form pre-implantation embryos; and, (3) embryonic germ cells (EG) derived from primordial cell lines of the post-implantation embryo. More recently, it has been shown that also stem cells in differentiated tissues can be multi- or even pluripotent.

1.2. Historical notes

Many of the advances in embryonic and adult stem cell research have been achieved by research using animal models, particularly mice, some dating back almost 40 years. Studies in the 1960s of teratocarcinomas in the testes of several inbred strains of mice resulted, for the first time, in the recognition of the pluripotent cell as a distinct type of cell. As will be shown below, teratocarcinomas, which are embryonal carcinomas (EC), are bizarre gonadal tumours containing a wide array of tissues derived from the three primary germ layers. In the mid-1970s, the suggestion arose that such pluripotent cells might provide a source of cells for therapy if cultured EC cell lines were obtained by isolating EC cells from teratocarcinoma. However, because of their tumoural origin, these cells were not considered an ideal basis for therapy. In 1989, attempts to derive a clonal line of human EC cells successfully showed that the behaviour of human EC clones differs from that of mouse ES or EG cells. The cells were aneuploid and their potential to differentiate spontaneously in vitro was limited.[5]

In 1981, research on embryonic stem cells became possible when researchers established culture conditions for growing mouse embryonic stem cells in the laboratory. They derived those stem cells from the inner cell mass of mouse blastocysts. The ES cells obtained yielded cell lines with normal diploid karyotypes and generated cell types characteristic for all three primary germ layers as well as primordial germ cells.[6] When injected into mice the ES cells induced the formation of teratomas.[7]

5 Pera MF, Coopers S, Mills J, and Parington JM. Isolation and characterization of a multipotent clone of human embryonal carcinoma cells. Differentiation 1989;42: 10-23.

6 Evans MJ, Kaufman, MH. Establishment in culture of pluripotential cells from mouse embryos. Nature 1981;292:154-6.

7 Martin GR. Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. Proc Natl Acad Sci USA 1981; 78: 7634-8.

It took nearly 20 years before investigators were, for the first time, able to isolate this class of pluripotent stem cell from early human embryos and foetuses and to grow them in culture. In November of 1998, James Thomson and his colleagues derived human ES cells from the inner cell mass of a normal human blastocyst donated by couples undergoing infertility treatment.[8] At the same time another group led by John Gearhart derived human embryonic germ (EG) cells from the gonadal ridge and mesenchyma of 5 to 9 weeks old foetal tissue that resulted from elective abortions.[9] From both sources, pluripotent stem cell lines were cultivated that were capable of self-renewing for long periods and of giving rise to many types of human cells. Since then, several research teams have tried to characterise many of the molecular characteristics of these cells and tried to improve on the methods for culturing and directing their differentiation into human tissues for transplantation purposes.

At about the same time, scientists were beginning to explore the so-called adult stem cells. These cells were thought originally to have a limited potential for production of differentiated derivatives. Yet, recent studies have shown that—in some circumstances—cells from one tissue can develop into cell types characteristic for other tissues. Adult stem cells have also been discovered in tissues of which it was previously thought they would not contain them, such as the brain. Such advances raise the question whether it could be possible to treat degenerative diseases, particularly neural diseases such as Parkinson's and Alzheimer's, as well as spinal cordon injuries, with adult stem cells and not only with ES cells.

Nevertheless, the possibility of isolating and cultivating stem cells—whether embryonic or adult stem cells—has raised hopes that such cells might be used in the treatment of patients. Tremendous research efforts are being made to further explore these possibilities.

1.3. Applications of stem cells

There are at least four broad applications of stem cells.

First: At the most fundamental level, stem cell research offers important information for developmental biology. It can help to identify the fundamental events during human development. A primary goal is the identification of the factors involved in cell specialisation. Some of the most serious medical conditions, such as birth defects and cancer are due to aberrations in cell specialisation and cell division. Another important area that links developmental biology to stem cell research is the knowledge of certain genes and factors that function during the development of the embryo. A better understanding of normal cell process will give better insights into the fundamental errors that cause these diseases.

8 Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, and Jones JM. Embryonic stem cell lines derived from human blastocyst. Science 1998; 282, 1145-7.

9 Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR, and Gearhart JD. Derivation of pluripotent stem cells from cultured human primordial germ cells. Proc Natl Acad Sci USA 1998; 95: 13726-31.

Second: Stem cells are already being explored as a vehicle for delivering genes to specific tissues in the body. In cancer research, for instance, cell lines are currently used in this way. Scientists are trying to discover more ways to use the specialised cells derived from stem cells to target specific cancerous cells and directly perform treatments that will destroy or modify them.

Third: The first potential application of human stem cells and their derivatives may be the testing of potentially therapeutic drugs. Stem cells will probably be used to develop pure populations of specific cell types for testing chemical compounds on material that can be used to treat the diseases related to those specific cell types. This would make it possible to explore the safety and efficacy of drugs before they are tested on animals and human subjects.

Fourth: Perhaps the broadest and most far-reaching potential application of human stem cells, based on their ability to give rise to a wide array of differentiated cell types, is the generation of cells and tissues. If stem cells can be grown and their development in cell cultures can be directed towards the cultivation of specialised cells, it may be possible to repair or replace cells or tissues that are damaged by degenerative diseases. This kind of therapy is sometimes called 'tissue engineering' or 'regenerative medicine'. Actually, the major focus of research is the generation of cells and replacement tissue for treating neurological diseases such as Parkinson's, Alzheimer's, multiple sclerosis and spinal cord injury. A major breakthrough in research on ES and adult stem cells has been the development of transplantable pancreatic tissues for treating diabetes (see 2.4.2).

1.4. The actual state of ES stem cell research

While stem cell research holds significant promises, there is still much to be done before this technology can be applied on a large scale in clinical practice. Stem cell research is still in its infancy and many fundamental questions remain unanswered. (Though in some cases, certain adult stem cells are being use in experimental treatment of patients).

If stem cells are to be used to treat human diseases, several challenges need to be met. Foremost is that stem cells will be needed in large quantities. Additionally, it must be possible to direct and control the differentiation of stem cells into the desired cell types.

At the present time, scientists are just beginning to direct the differentiation of stem cells into the cell types needed for transplantation and to identify the functional capacities of the resulting specialised cells. Whereas differentiated cells generated from mice embryonic and adult stem cells seem to be able to repair or replaced damaged cells and tissues, human stem cell populations appear to multiply more slowly and to differentiate more readily. To date, particularly given the very early stage of the science of stem cell biology, it is impossible to predict whether the same results could be obtained with humans. The answer clearly lies in conducting more research.

In this chapter the state of the art with respect to research on stem cells from different sources will be described.

2 SOURCES OF STEM CELLS AND THEIR PROPERTIES

Human pluripotent stem cells are derived from different sources. We describe the four main sources.

2.1. Teratomas

Teratomas or teratocarcinomas are benign tumours containing an aberrant mix of tissues derived from all three primary germ layers of the embryo.[10] They typically contain gut-like structures such as layers of epithelial cells and smooth muscle, skeletal or cardiac muscle (which may contract spontaneously), neural tissue, cartilage or bone and sometimes hair.

The differentiated cells of the tumour are formed from undifferentiated cells, termed 'embryonal carcinoma' (EC) cells also present in the tumour. EC cells are themselves derived from primordial germ cells (PGCs), the embryonic precursors of the gametes.[11]

The ability of EC cells to give rise to different tissue types appears to be limited. They only generated a few kinds of cells types they remain undifferentiated when grown at high density.[12] This could be due to the fact that, because of their tumour origin, EC cells may carry genetic variations linked to tumour genesis that restrict their capacity of differentiation.

2.2. Embryonic stem cells (ES)

Characteristics of embryonic stem cells

Embryonic stem cells can be derived from the pluripotent inner cell mass (ICM) of the pre-implantation blastocyst stage 5-days human embryos. Embryos used as a source for stem cells are generally surplus embryos of IVF-techniques or embryos generated solely for research purposes. At this stage, a human embryo consists of 200 to 250 cells. Most of the cells comprise the trophectoderm. For deriving ES cell cultures, the trophectoderm is removed. At this stage the inner cell mass is composed of only 30 to 34 cells.[13]

Embryonic stem cells are scientifically valuable because they have two unique properties. First, they have the enzyme telomerase[14] and can replicate indefinitely while retaining a normal karyotype for two years through 300

10 Stevens LC. The biology of teratomas. Adv Morphogen 1967; 6: 1-31.

11 Stevens LC. Origin of testicular teratomas from primordial germ cells in mice. J Natl Cancer Inst 1967;38:549-52.

12 Andrews PW. Teratocarcinomas and human embryology: pluripotent human EC cell lines. Review article. APMIS 1998;106:158-67.

13 Bongso A, Fong CY, Mathew J, Ng LC, Kumar J, and Ng SC. The benefits to human IVF by transfering embryos after the in vitro embryonic block: alternatives to day 2 transfers. Asst Reprod Rev 1999.

14 Betts DH, King WA. Telomerase activity and telomere detection during early bovine development. Genet 1999;25:397-403.

population doublings.[15] All the descendants of an ES cell constitute an embryonic stem cell line. Second, these cells are pluripotent. Depending on the culture conditions, ES cells may form clumps of cells that can differentiate spontaneously to generate different cell types derived from all three primary germ layers: cardiomyocits, hematopoietic precursors, skeletal myocyts[16], muscle cells, adipocyts[17], condryocits[18], endoterial cells[19], melanocyts[20], neurons, cell from the pancreatic islets[21] and glial cells.[22] These cells appear to have the ability of maintain their pluripotent character even after 4 to 5 months of culturing.

Potential applications of embryonic stem cells

Based on the present state of scientific knowledge, ES cells appear promising for therapeutic applications because they seem to combine properties not found together in other cell lines. They are easier to isolate, they are likely to be more plastic than other stem cells and they replicate indefinitely without undergoing senescence. The regenerating potential of the ES seems to be very extensive. If they can be grown and their development can be directed in cell culture, ES cells can then be used for transplantation purposes in the treatment of degenerative diseases such as Parkinson's, diabetes, heart failures, and some forms of cancer.

ES cells are also scientifically valuable as an important tool for elucidating the mechanism of development and cell differentiation. Some biologists consider embryonic stem cell research as the only window that offers insights into the earliest stages of human development that cannot be studied directly in the human embryo in utero or fully understood through the use of animal models. Such research can have important clinical consequences for birth defects, infertility, and pregnancy loss. This understanding of normal development will ultimately allow the prevention or treatment of abnormal human development.

In addition, ES cell research can help scientists understand how egg cytoplasm can reprogram a nucleus. That knowledge could allow reprogramming the patient's somatic nucleus leading to ES cells without any need for eggs or embryos.

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15 Odorico JS, Kaufman DS and Thomson JA. Multilineage differentiation from human embryonic stem cell lines. Stem Cells 2001;19:193-204.

16 Doetschman TC, Eistetter H, Katz M et al. The in vitro development of blastocyst derived embryonic stem cells lines: formation of visceral yolk sac, blood islands and myocardium. J Embryol Exp Morphol 1985;82:27-45.

17 Dani C. Embryonic stem cell-derived adipogenesis. Cells tissues Organs 1999;165:173-80.

18 Poliars A, Nifuji A, Lamblin D et al. Controlled conversion of an immortalized mesodermal progenitor cell towards osteogenic, chondrogenic, or adipogenic pathways. Cell Biol 1995;130:1461-72

19 Risau W, Sariola H, Zerwes HG, et al. Vasculogenesis and angiogenesis in embryonic-stem-cell-derived embryonic bodies. Development 1995 ;102:471-8.

20 Yamane T, Hayashi S, Mizoguchi M et al. Derivation of melanocytes from embryonic stem cells in culture. Dev Dyn 1999 ;216:450-8

21 Soria B, Roche E, Berna G et al. Insulin-secreting cells derived from embryonic stem cells normalise glycemia in streptozotocin-induced diabetic mice. Diabetes 2000;49:157-62.

22 Brustle O, Jones KN, Learish RD et al. Embryonic stem-cell-derived glial precursors: a source of myelinating trnasplants. Science 1999;285:754-6

So far research with embryonic stem cells in vivo is still in the animal testing stage but some results obtained with mouse ES cells seem to be promising. Cardiomyocytes selected in culture from mouse ES cells could form apparently functioning intracardiac grafts that repaired heart cells in mouse.[23] Injection of mouse ES cell-derived precursors in rats with MS (Multiple sclerosis) led to the formation of myelin in the brain and spinal cord.[24] Although experiments have shown that derivatives of ES cells can be transplanted successfully to animal models of diseases in which they function as their in vivo counterparts do[25], only very few were able to demonstrate the possibility of a single ES cells to give rise in vitro to different cell types.[26] This often makes it impossible to know when the results of an experiment or a therapeutic intervention can be attributed to the added stem cells or to cells already present in the recipient.

Currently, the only test for the in vivo pluripotency of human ES cells that has been performed is to inject them into immunodeficient mice and rats. In the first report using human ES cells for transplantation, rats with a diffuse motor neuron injury showed partial recovery of motor function. A critical aspect in this experiment is that the ES cells were injected directly after the inducement of the paralysis and they did not present some of the symptoms that are typical in patients having such a disorder for a long time.

One of the first to demonstrate the capacity of ES cells to improve a degenerative disease was a USA research team that succeeded in reversing the symptoms of Parkinson's disease in rats using ES cells isolated from mice. The ES cells were treated in order to express molecular, morphological and functional features specific for midbrain dopamine-neurons and injected into the brain of rats with Parkinson's symptoms. The animals stopped running in circles and survived for 2-3 months. Although these results are promising, it cannot be concluded that human ES cells will function in a similar way.[27] Dramatic differences in primate and rodent development of specific lineages limits the adequacy of mouse ES cells as a model for human ES cells.

Zhang and co-workers at the University of Wisconsin, Madison have demonstrated the ability of human ES to develop into nascent brain cells and further develop into healthy, functioning neural cells.[28] They transplanted stem cells taken from early human embryos into the brains of baby mice where they developed into neurons and astrocytes, the cell species that populate the different regions of the brain and spinal cord. An important result of this work is the complete absence of teratomas or tumours in the mice that received the

23 Klug MG, Soonpaa MH, Koh GY, and Field LJ. Genetically selected cardiomyocytes from differentiating embryonic stem cells form stable intracardiac grafts. J Clin Invest 1996;98:216-24.

24 Brustle O et al. Embryonic stem cell-derived glial precursors: a source of myelinating transplant. Science 1999;285:754-6.

25 Lee SH, Lumelsky N, Studer L, Auerbach JM, and McKay RD. Efficient generation of midbrain and hindbrain neurons from mouse embryonic cells. Nat Biotechnol 2000;18:675-9.

26 Lumelsky N, Blondel O, Laeng P, Velasco I, Ravin R, and McKay R. Differentiation of Embyonic stem Cells to Insulin-Secreting Structures Similar to Pancreatic Islets. Science 2001;292:1389-94.

27 McKay R et al. Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. Nature 2002;418:50-6

28 Zhang SC, Werning M, Ducan ID, Brustle O, Thomson JA. In vitro differentiation of transplantable neural precursors from human embryonic stem cells . Nature Biotechnologie 2001;19:1129-32

cell transplants. These results may be an indication that human embryonic stem cell development can be steered to specialised cell types in vitro, and that they can be transplanted into animals for further development into the cell types necessary for normal development. However, in early experiments realised by Geron researches in California, the human ES did not really differentiate into brain cells. Instead, they stayed in a disorganised cluster and brain cells near to them began to die. So more research must be done to know how to direct the cells to differentiate into the desired cell type before this technology can be tried on humans..

Problems linked to ES cells

If ES cells are to be used to treat human diseases, several significant challenges must be overcome before the technology can be applied in clinical practice.

1) The capacity of ES cells to divide indefinitely can lead to the formation of tumours. There is concern also that human ES cells could undergo hyperproliferation[29] leading to the development of benign tumours and consequently into cancerous growth. After injection of human ES cells in immune-deficient mice, they have formed teratomas with many cell types. Experiments in mice detected altered allelic methylation patterns of the DNA that persisted on in vivo differentiation to foetal stages.[30] Culturing ES cells affects their totipotency and may be associated with deregulation of genomic imprinting that affects the potential for these cells to develop into normal foetuses.[31] So, there is a double risk of tumour development: ES are themselves tumourogenic when they are not differentiated and the gene expression of the ES cell genome seems to be extremely unstable.
2) ES cells have the tendency to differentiate spontaneously and scientists have not yet developed the techniques to control the specialisation process by which to direct them into the desired cell type. Under certain culture conditions ES cells differentiate but do so into a random, mixed population of different cell types. In addition, there is significant variability in the development of a particular phenotype under identical growth factor conditions.[32] Rarely have specific growth factors or culture conditions led to the establishment of cultures containing a single cell type.[33] Many of the factors required for the correct differentiation of embryonic cells are not chemicals that can readily be added to the culture medium. Cells require

29 Shamblott MJ, Axelman J, Littlefield JW, Blumenthal PD, Huggins GR, Cui Y, Cheng L, and Gearth JD. Human embryonic germ cell derivates express a broad range of developmentally distinct markers and proliferate extensively in vitro. Proc Natl Acad Sci USA 2001; 98: 113-8.

30 Dean W, et al. Altered imprinted gene methylation and expression in completely ES cell-derived mouse foetuses: association with aberrant phenotypes. Development 1998 ;125:2273-82.

31 Khosla S, et al. Culture of preimplantation mouse embryos affects foetal development and the expression of imprinted genes. Biology of Reproduction 2001;64:918-26.

32 Odorico JS, Kaufman DS, Thomson JA. Multilineage differentiation from human embryonic stem cell lines. Stem Cells 2001;19:193-204.

33 Schuldiner M, et al. Effects of eight grwoth factors on the differentiation of cells derived from human embryonic stem cells. Proc Natl Acad Sci USA 2000;97:11307-12

factors such as mechanical tension, large-scale electric fields, or complex structural environments provided by their embryonic neighbours in order to activate appropriate genes and maintain normal gene expression patterns. Providing the structural nonmolecular factors required to get the differentiated cells is quite difficult. The absence of these mechanical factors could easily generate cells that appear to be normal but are in fact abnormal. As a consequence, so far it is not possible to produce pure cultures of the cell types that are required for safe and reliable cell therapies.

3) Keeping human ES cells alive can be a challenge. They seem to be tricky and tedious to grow.[34] To date, it is unproven whether cells derived from 64 individual genetically diverse blastocysts are viable. Of the 19 colonies made at the University of Göteborg (Sweden) only three lines have been held alive for about six months and their potential to turn into all the major cell types of the body has not yet been demonstrated. Twelve colonies have been kept alive for less than three months and the viability of four other colonies has not yet been tested.

4) Early evidence from research on human embryos raised the possibility that ES cells might be unrecognisable to the immune system. Current experiments have shown that undifferentiated human ES cells had a very low, but consistent expression of MHC-class-1.[35] Because of this, ways to prevent the immune system from rejecting transplanted cells must also be developed. Immune suppression, tolerance induction and banking ES cells with records of genetic compatibility or genetically altered cells to reduce or combat immune rejection are possible solutions for overcoming this problem.

5) Human ES cells required either foetal calf serum or a conditioned medium produced by mouse feeder cells for their growth.[36] This increases the risk of contamination with infectious agents that could be present in bovine serum, when using cells form cultures that were established that way.

6) As mentioned before, the principal source of ES cells are the spare embryos obtained by IVF. Apart from the ethical issues related to the use of human embryos (see next chapter), women who are IVF embryo donors undergo an ovarian stimulation that can lead to abnormalities in the egg cells. These abnormalities could be also present in the stem cells of the derived embryos.

Given these observations, it is uncertain whether ES cells can be used for transplants or other therapeutic applications. To date, ES cells have not helped a single ill person. In some Parkinson's disease patients, the transplant of embryonic stem cells has even produced negative results, worsening the patient's condition rather than improving it.[37] There is no evidence so far that cells generated from embryonic stem cells can be safely transplanted back into

34 Vogel G. Stem cells: new excitement, persistent questions. Science 2000;290:1672-4.

35 Drukker M and Benvenisty N. Embryonic stem cells not so stealthy after all. Science. Public on line July 5, 2002

36 Xu C et al. Feeder-free growth of undifferentiated human embryonic stem cells. Nature 2001;19:971-4.

37 Freed CR, Green PE, Breeze RE.. Transplantation of embryonic dopamine neurons for severe Parkinson' s disease. N Engl J Med. 2001; 33: 710-5.

adult animals to restore the function of damaged or diseased adult tissues. The level of scientific rigor that is normally applied in the development of potential medical treatments seems to be under pressure in this field.

Finding ways to direct undifferentiated ES cells to become specific cell types is an important first step required before new therapies can be developed. Prior to bringing ES cells to the clinic, other fundamental questions that must be addressed experimentally are (a) how can we make sure that they do migrate to the right sites, and (b) do not go to the wrong place, and (c) what is the most adequate differentiation stage of cells to be used in transplantations?

2.3. Germinal stem cells from aborted foetuses

Germinal stem cells

Human germinal (EG) stem cells are pluripotent cells derived from the primordial germ cells (PGCs) of a specific part of the embryo/foetus called gonadal ridge, which normally develops into mature gametes (egg and sperm). Specifically they are isolated from the 5- to 10-week old foetus. In the presence of serum and some growth factors, PGCs form colonies of cells that are morphologically indistinguishable from EC cells or ES cells cultures.[38]

The process of growing pluripotent cells derived from human EG cells requires the generation of embryonic bodies (EB), which consist of an unpredictable mix of partially differentiated cell types. These embryonic bodies have a high proliferative capacity and gene expression patterns that are representative of multiple cell lineage.[39] This suggests that they are progenitor cells for a variety of differentiated cell types.

Although EG cells are capable of long term self-renewal, like ES cells, they appear to divide less readily than ES cells. While ES cells could proliferate for 300 populations doublings, most EG cells proliferate for 40 doublings. The maximum reported until now is 70 to 80 population doublings.[40]

EG cells differ from ES cells also in their behaviour in vivo. While ES cells injected into immunocompromised mice generate teratomas with different cell types, EG cells do not.[41]

38 Donovan P, Gearthart J. The end of the beginning for pluripotent stem cells. Nature 2001;414:92-7.

39 Shamblott MJ, Axelman J, Littlefield JW, Blumenthal PD, Huggins GR, Cui Y, Cheng L, Gearthart JD. Human embryonic germ cell derivatives express a broad range of developmentally distinct markers and proliferate extensively in vitro. Proc Natl Acad Sci USA 2001;98:113-8.

40 Shamblott MJ, Axelman J, Littlefield JW, Blumenthal PD, Huggins GR, Cui Y, Cheng L, Gearthart JD. Human embryonic germ cell derivatives express a broad range of developmentally distinct markers and proliferate extensively in vitro. Proc Natl Acad Sci USA 2001;98:113-8.

41 Itskovitz-Eldor J, Schuldiner M, Karsenti D, Eden A, Yanuka O, Amit M, Soreq H, and Benvenisty N. Differentiation of human embryonic stem cells into embryonic bodies comprising the three embryonic germ layers. Mol Med 2000;6:88-95.

Therapeutic potential

Although the available scientific data about the potential applications of EG cells are scant, some experiments have been realised in mice and humans.

Human EG cell derivatives have been shown to cause improvement in paralysed rats. Three months after the injection of EG cells into the fluid surrounding the spinal cord of partially paralysed rats, many of them were able to move and walk. However, it is not yet clear whether the human EG cell derivatives replaced the damaged spinal motor neurons or whether the injected cells triggered neurons in the recipient animals to recover lost function.[42]

EG cells are also used for research on treatment of Parkinson's disease. Injecting EG cells, previously treated to produce high levels of dopamine, leads to a reduction in the Parkinson's symptoms in mice. However, the results obtained in human subjects are few and not satisfactory. In some experiments with patients a stable increment of 20% in the production of dopamine has been observed in the patients that were younger than 60 years. Nevertheless, 15% of the patients older than 60 developed uncontrolled flailing movements due to an hyperpoliferation of foetal cells.[43]

Actually several groups of researchers are investigating the use of foetal tissue as a potential source of stem cells for treatment of diseases such as diabetes. Some current experiments have shown that foetal bone marrow cells are much more effective than adult bone marrow and umbilical cord blood cells. It appears that foetal bone marrow cells do not provoke an immune reaction to the same degree as do adult or newborn infant cells. This applies both when the unborn child is the donor and when he or she is the recipient. That is, foetal cells can be used to treat adults, or adult bone marrow cells can be used to treat a child in the womb without the usual risk of immune reactions.

Although the findings provide a compelling demonstration of the potential of human EG cells, the limited growth characteristics and difficulties associated with their isolation would make extensive experimental manipulation difficult. For foetal cells to be useful in transplantations, they must be old enough to 'know' of which kind of tissue they will be part, but young enough to be not too specialised yet to be able to develop into the specific cell type that is needed.

Another question that remains to be answered is whether EG cells are genetically stable and safe. Spontaneous and some 'therapeutic' abortions may be due to genetic abnormalities, implying that cells isolated from those foetuses could carry genetic defects.

42 Kerr DA, Llado J, Shamblott MJ, Maragakis N, Irani DN, Dike S, Sappington A, Gearthart JD, and Rothstein, J. Human embryonic germ cell derivatives facilitate motor recovery of rats with diffuse motor injury. 2001

43 Feed CR, Green PE, Breeze RE Tsai WY, DuMouchel W, Kao R, Dillo S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, and Fahn S. Transplantation of embrionic dopamine neurons for severe Parkinson's disease. N Eng J Med 2001;33:710-9.

2.4. Adult stem cells

2.4.1. General characteristics of adult stem cells

As already noted above, stem cells have also been found in some types of adult tissue. An adult stem cell is a partially differentiated cell that is found in a specialised tissue in the body of adults and in foetuses. The primary functions of adult stem cells are to maintain the steady state functioning of a cell and to replace cells that die because of injury or of disease.[44]

Like all stem cells, adult stem cells can divide and retain their characteristics (self-renewal) during long periods. In addition, they can give rise to a variety of mature cell types with specialised functions. Adult stem cells are thought to be multipotent. They can give rise to several terminally differentiated cell types constituting a specific tissue or organ and usually have a limited time span.

Adult stem cells usually develop into progenitor or precursor cells; these are partly differentiated cells that divide and give rise to mature specialised cell types. Progenitor cells differ from adult stem cells in that the former divide to form more progenitor cells or two specialised cells, neither of which is capable of replicating itself. In contrast, when a stem cell divides, one of the two generated cells is often a stem cell capable of replicating itself again.[45]

Sources of adult stem cells and their potential

Until recently, adult stem cells were thought to have a more limited potential to produce differentiated derivatives than ES cells and EG cells because they are further developed and specialised and are already committed to develop into particular cell types. However, current research in animals is leading scientists to question this view.

The list of adult tissues that have been shown to contain stem cells is currently growing. To date, stem cells have been identified in bone marrow, blood, the cornea and retina of the eye, the dental pulp of the tooth, liver, epithelia of the skin, brain, skeletal muscle, spinal cord gastrointestinal tract, and pancreas. A short description of main sources is given below.

Bone marrow and peripheral blood stem cells

Bone marrow has been used as source of hematopoietic stem cells for more than 40 years.[46] Until recently, bone marrow cells were recognised only as a potential source of cells for reconstituting the blood or immune system. However, more recent experiments with rats indicate that stem cells found in bone marrow might be as flexible as embryonic stem cells and can possibly form any cell type. They can be grown in culture for long periods of time and still retain their plasticity. Mouse studies have found that bone marrow cells

44 Holtzer, H. (1978) Cell lineages, stem cells and the ' quanta' cell cycle concept. In Stem cells and tissue homeostasis. Eds: B.I. Lord, C.S. Potten, and R.J. Cole. (Cambrigde,New york; Cambridge University Press), 1-28.

45 National Institutes of Health. Stem cells: scientific progress and future research directions. 2001;ES-3.

46 Till JE and McCullough EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat Res 1961;12:213-22

can be used to regenerate liver[47], kidney[48], lung, intestine, muscle, and skin[49] and to restore damaged heart tissue. Recently it has been shown that bone marrow implantation can increase angiogenesis in a rat heart attack model system.[50] The ability to form muscle tissue opens up a whole new avenue of potential therapies for muscular dystrophy.

Results of clinical trials conducted recently in England[51], Germany[52] and Brazil[53] in which stem cells isolated from the patient's own bone marrow were injected in the damaged area resulted in a improvement of heart function within weeks. These results suggest that transplantation of human adult autologous adult stem cells from bone marrow can lead to the regeneration of the myocardial scar after infarction. Since all reported attempts of clinical cell transplantation for myocardial regeneration have been done in association with interventional revascularisation, further studies are needed to clarify the role of cell transplantation in myocardial regeneration.

A small number of hematopoietic stem cells proceeding from bone marrow circulates normally in the blood stream. By injecting the donor with a cytokine such as granulocyte-colony stimulating factor, stem cells can be stimulated to migrate from bone marrow to blood in greater numbers. Hematopoietic stem cells from peripheral blood can be used to repopulate an ablated bone marrow in cancer treatments, fat cells, and cartilage and bone cells. They show some advantages over bone marrow including a high rate of engraftment, rare contamination with latent viruses. They are easier to isolate from the patient and seem to give better results in transplants. Patients receiving peripherally harvested stem cells have higher survival rates than patients receiving bone marrow cells. These cells have been successfully used in autologous cell transplantation in breast cancer patients to recover blood cells after intensive chemotherapy.[54]

One of the most exciting properties of hematopoietic stem cells is that they show anti tumour activity against some types of tumours. Peripherally collected

47 Petersen BE, Bowen WC, Patrene KD et al. Bone marrow as a potential source of hepatic oval cells. Science 1999 ;284:1168-70.

48 Poulson R, et al. Bone marrow contributes to renal parenchymal turnover and regeneration. Jour Of Pathol 2001;195:229-35.

49 Alison MR, Poulson R, Jeffery R, et al. Hepatocytes from non-hepatic adult stem cells. Nature 2000;406:257.

50 Kamihata H, et al. Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral perfusion and regional function via side supply of angioblasts, angiogenic ligands and cytokines. Circulation 2001;104:1046.

51 Galinañes M, Loubani M, Davies J, Chin D, Pasi J, and Bell P. Safety and efficacy of transplantation of autologous bone marrow into scarred myocardium for the enhancement of cardiac function in man. Circulation 2002;106, published on line October 15, 2002 supplement II-II-463

52 Stamma C, Westphala B, Kleineb HD, Petzsch M, Kittnerd C, Kingea H, Schümichend C, Nienaberc CA, Freundb M, Steinhoof G. Autologous bone-marrow-stem-cell transplantation for myocardial regeneration. The Lancet 2003;361:45-6

53 Perin EC, Dohmann HFR, Borojevic R, Silva SA, Sousa ALS, Mesquita CT, Rossi MID, Cravlho AC, Dutra, HS, Dohmann HJF, Silva GV, Belém L, Vivacqua R, Rangel FOD, Esporcatte R, Geng YJ, Vaughn WK, Assad, JAR, Mesquita ET, and Willerson JT. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation 2003;107(18):2294.

54 Negrin RS, Atkinson K, Leemhuis T, Hanania E, Juttner C, Tierney K, Hu WW, Johnston LJ, Shizum JA, Stockerel-Goldstein KE, Blume KG, Weissman IL, Bower S, Baynes R, Dansey R, Karanes C, Peters W, and Klein J. Transplantation of highly purified CD34+Thy-1+ hematopoietic cells in patient with metstatic breast cancer. Biol Blood Marrow transplant 2000;6:262-71.

hematopoietic stem cells have also been used to treat metastatic kidney cancer, showing reduction of tumours in half the number of patients treated. A problem with the use of autologous hematopoietic blood cell transplants in cancer therapy has been that sometimes cancer cells are collected and re-infused back into the patient along with the stem cells. Methods to purify the cells have now been developed. A disadvantage of peripheral blood stem cells is that they are more likely to cause graft versus host disease than would cells from bone marrow.

Blood stem cells may be able to differentiate into another mesodermally derived tissue, such as skeletal muscle[55] and also to give rise to neural tissue, which is derived form embryonic ectoderm.[56]

Human mesenchymal stem cells (MS cells), required for the maintenance of bone, muscle, and other tissues, have been isolated from bone marrow and peripheral blood.[57] These cells are found at a frequency of approximately 1/100.000 nucleated cells in bone marrow but methods have been developed by which this minor fraction of cells can be isolated and expanded into billions of cells.[58] Transplanted mesenchymal stem cells isolated from bone marrow restored the function of limbs in rats after stroke injuries to their brains. The transplanted stem cells exhibited characteristics of different types of neural cells, such as astrocytes, oligodendroglia and neurons.[59]

Work of Ray Chiu of McGill University in Montreal indicates that the mesenchymal cells injected into rats seem to go only to damaged areas and can turn into heart muscle, blood vessels, fat cells, cartilage, bone and fibrous tissue. Mouse studies suggest their potential may be greater, perhaps even including neural cells.[60] Experts in stem cell research believe that these cells may allow for tissue replacement in patients suffering from cancer, osteoporosis, dental disease, or injury.

Mesenchymal stem cell-based bone regeneration has been demonstrated in various animal models. Use of this therapy in the clinic has been successful for dental applications.[61]

Recent investigations show that mesenchymal stem cells from adults do not carry the markers on their surface (MHC Class II molecules or de co-

55 Ferrari G, Cusella-De Angelis G, Coletta M, Paolucci E, Stornaiuolo A, Cossu G, and Mavilio F. Muscle regeneration by bone marrow-derived myogenic progenitors. Science 1998;279:1528-30.

56 Brazelton TR, Rossi FM, Keshet GI, and Blau HM. From marrow to brain: expression of neuronal phenotypes in adult mice. Science 2000;290:1775-9.

57 Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas RJ, Moorman M, Simonetti D, Craig S, and Mrshak DR. Multilineage Potential of Mesenchymal Stem Cells. Science 1999;284:143-7.

58 Livingston TL, Gordon S, Archambult M, Kadiyala S, McIntosh K, Smiths A, and Peter SJ. Mesenchymal stem cells combined with biphasic calcium phosphate promote bone regeneration. Jor of Materials Science 2003; materials in medicine 14:211-8.

59Li-Ru Zhao, Wei-Ming Duan, Morayma Reyes C, Dirk Keene, Catherine Verfaillie M and Walter Low C. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grating into the ischemic brain of rats. Experimental Neurology 2002;174:11-20.

60 Pagán Westphal S. One cell to heal them all. Newscientist 2002;172(2321):15.

61 Livingston TL, Gordon S, Archambult M, Kadiyala S, McIntosh K, Smiths A, and Peter SJ. Mesenchymal stem cells combined with biphasic calcium phosphate promote bone regeneration. J of Materials Science 2003; materials in medicine 14:211-8.

stimulatory molecules B7, CD40) that lead to trigger immune rejection by activating T cells.[62] This property could make possible the use of stem cells from different donors other than the patient. Furthermore, these cells do not form tumours when transplanted into the patient, as sometimes happens with embryonic stem cells.

Obtaining MS cells should be relatively easy. They do not grow indefinitely in culture but from a single bone marrow donation enough cells can be grown to treat 10,000 people or more.

Brain and central nervous system cells

Although according to conventional medical wisdom the adult central nervous system of the human being does not contain stem cells, there is now widespread consensus that the adult mammalian brain does contain such cells. For instance, neuronal stem cells that could give rise to blood, muscle, intestine, liver and heart cells have been isolated from the rat and mouse nervous system. Unlike bone marrow stem cells, stem cells from the central nervous system do not occur in a single location, which makes it difficult to isolate them. Because so far no markers are known to identify the cells in vivo, the only way to test the presence of CNS cells is to isolate these cells and manipulate them in vitro which may change their intrinsic properties.[63] Actuallytwo groups of adult central nervous system stem cells in human brain have been found: cells of the ventricular and subventricular zone of the brain[64] and cells of the hippocampus.[65]

Astrocytes of the subventricular zone have the ability to form neurospheres that can differentiate into neurons and glial cells.[66] Ependymal cells in the ventricular zone might have the potential to generate olfactory bulb neurons in vivo.[67]

The region of the hippocampus in which stem cells apparently exist in mouse and human brains is the subgranular zone of the dentate hyrus.[68] Under the right growth conditions stem cells from the hippocampus could develop into normal neurons that produce neurotransmitters and that form synapses with the normal neurons.[69]

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62 Devine SM, Peter S, Martin BJ, Barry F, McIntosh KR. Mesenchymal stem cells: stealth and suppression. Cancer J 2001;7 Suppl 2:S76-82.

63 Morrinson SJ, White PM, Zock C and Anderson DJ. Prospective identification, isolation by flow cytometry, and in vivo drlf-renewal of multipotent mammalian neural crest stem cells. Cell 1999; 96: 737-49.

64 Morshead CM and van der Kooy KD. A new 'spin' on neural stem cells? Curr Opin Neurobiol 2001;11:59-65.

65 Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA,Gage FH. Neurogenesis in the adult human hippocampus. Nat Med 1998; 4: 1313-7.

66 Doetsch F, Caille I, Lim DA, García-Verdugo JM, and Álvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 1999;97:703-16.

67 Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, and Frissen J. Identification of a neural stem cell in the adult mammalian central nervous system. Cell 1999;96:25-34.

68 Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA and Gage FH. Neurogenesis in the adult human hippocampus. Nat Med 1998;4:1313-7.

69 Stevens CF, Song H, and Gage F. Advance on line article in Nature Neuroscience, 2002

A type of cell that may be a neuronal stem cell has been isolated from adult brain tissue that was surgically removed from a piece of brain tissue of a Parkinson's patient. The patient, a 57-year old man, is still without symptoms three years after the adult neural stem cells were removed from his brain, coaxed into becoming dopamine-producing cells, and then reimplanted. The treatment reduced the symptoms of the disease by more than 80%. Because the stem cells came from the patient, there was no need for immunosuppression to overcome rejection. In addition to its use for Parkinson's disease the technique is under study for juvenile diabetes, stroke, brain tumours, spinal cord injury, and other conditions.[70] In the experiments reported so far neural stem cells cultured from adult brain tissue may differentiate to form haematopoietic cells.[71]

Using adult neural stem cells, Michel Levesque, at the Cedars-Sinai Medical Center in Los Angeles, reports a total reversal of symptoms in the first Parkinson's patient treated.

In contrast, mouse ES cells injected in rats showed a modest benefit in 50% of the rats, but a 20% of them died of brain tumours.[72] In addition to its use for Parkinson's disease, the transplantation of human neural stem cells could potentially provide a way to repair tissue damaged by other neurodegenerative diseases such as Alzheimer, stroke, brain tumours, spinal cord injury, and epilepsy.[73] Recent experiments with mice suggest that when neural stem cell are placed into the bone marrow, they appear to produce a variety of blood cell types.

Skeletal muscle stem cells

Al least three populations of skeletal muscle stem cells have been identified: satellite cells, cells in the wall of the dorsal aorta and the cells known as 'side-population' cells.

Although satellite cells do not divide normally, they give rise to myogenic precursors when the muscle is damaged as a result of injury or weight-bearing exercise. This suggests that satellite stem cells isolated from a patient and injected into the damaged muscle tissue could regenerate the muscle function.[74]

Human myoblast precursors have already been used successfully for the regeneration of heart function of a 72 year-old patient with ischaemic cardiac

70 Levesque M. Results presented April 8th, at the meeting of the American Association of Neurological Surgeons. Source: The World's No.1 Science & Technology News Service; 18 April 02, 12:30

71 Bjornson, C.R., Rietze, R.L., Reynolds, B.A., Magli, M.C., and Vescovi, A.L. Turning brain into blood: A hematopoietic fate adopted by adult neural stem cells in vivo. Science (1999); 283:534-537.

72 Bjorkulund LM. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc Natl Acad Sci USA

73 Lévesque MF and Neuman T. Communication at the annual meeting of the American Association of Neurological Surgerons (AANS) in Chicago at April 8, 2002

74 Beauchamp JR, Morgan JE, Pagel CN, Partridge TA. Dynamics of myoblast transplantation reveal a discrete minority of precursors with stem cell-like properties as the myogenic source. J Cell Biol 1999;144:1113-22.

muscle. One month after transplantation a notable recovery of heart function was observed.[75]

Experiments with human side-population cells showed that they could have the ability to restore the expression of dystrophin when injected into a mouse in which Duchenne's muscular dystrophy had been induced.[76]

Pancreatic stem cells

Stem cells in the pancreas are assumed to be in the pancreatic ducts or in the islets themselves.[77] Experiments with ductal cells isolated from adult human pancreatic tissue have shown the capacity of these cells to differentiate into clusters that contain both ductal and endocrine cells. Although these cells could not grow indefinitely, they could be expanded. The insulin production of these cells appeared to be proportional to the amount of glucose in the medium: higher glucose concentrations, lead to an increase in insulin production.[78] This indicates that it might be possible to proliferate ductal cells removed from a patient who lacks functioning beta cells but whose duct cells remained intact, and insert them back.

Ductal tissue can also be taken from human cadavers and grown in culture to form functioning pancreatic islet cells.[79]

Stem cells in the thymus

Stem cells have also been identified in the thymus. Very few starting stem cells seem to be able to regenerate a fully functioning organ, regenerating the production of T-cells. These stem cells could be used for regenerating the immune system after radiation therapy or chemotherapy and for treatment of diseases in which T-cells are severely depleted such as AIDS. It could also be used in controlling organ transplantation and correcting auto-immune diseases.[80]

Stem cells in the olfactory bulb

Stem cells found in the olfactory bulb of humans could give rise to neurons, oligodendrocytes and astrocytes, depending on the culture conditions and the growth factors in the medium. Nerve cells called olfactory ensheathing glia

75 Menasche P, Hagege AA, Scorsin M. Myoblast transplantation for heart failure. Lancet 2001;357:279-80.

76 Gussoi E, Soneoka Y, Strickland CD,Buzney EA, Khan MK, Flint AF, Kunkel LM, and Mulligan RC. Dystrophin expression in the mdx mouse restored by stem cell transplantation. Nature 1999;401:390-4.

77 Zulewski H, Abraham EJ, Gerlach MJ, Daniel PB, Moritz W, Muller B, Vallejo M, Thomas MK, Habener JF. Multipotential nestin-positive stem cells isolated from adult pancreatic islets differentiate ex vivo into pancreatic endocrine, exocrine,and hepatic phenotypes. Diabetes 2001; 50: 521-33

78 Bonner-Weir S, Taneja M, Weir GC, Tatarkiewicz K, Song KH, Sharma A, and O'Neil JJ. In vitro cultivation of human islets from expanded ductal tissue. Proc Natl Acad Sci USA 2000;97:7999-8004.

79 Berger A. Transplanted pancreatic stem cells can reverse diabetes in mice. British Medical Journal 2000;18:736.

80 Gill J, Malin M, Holländer GA, Boyd R. Generation of a complete thymic microenvironment. Nature Immunology 2002; 3: 635-42.

taken from the olfactory bulb and injected into the spine of paraplegic rats have shown the ability to promote the re-growth of cells across the gap in the spine.[81]

Research on human spine repair has had limited results with only partial recovery of movement. But the results give scientists hope that further research could bring success. Current research investigates the possibility of using stem cells drawn from olfactory bulb to treat neurodegenerative diseases such as Parkinson's disease, Alzheimer, multiple sclerosis and brain injuries. These stem cells could also be harvested from cadavers[82] and coaxed to differentiate into neurons that can be injected into patients.

Epithelial stem cells of the skin

The skin of mammals seems to contain different stem cells in the epidermis, in the hair follicle and in the glandular epithelium.[83] These stem cells are responsible for epithelium renewal. The replacement pattern for stem cells in each compartment differs. Stem cells of the bulge region of the hair follicle appear to give rise to multiple cell types in the hair follicle and also to the epidermis of the skin.[84] This ability makes these stem cells particularly interesting for use in the treatment of skin diseases such as skin cancer and psoriasis. Other scientists have been able to induce skin cells isolated from a patient to behave as immune system cells and nerve cells.

Stem cells from oesophageal epithelium

The epithelial basal layer consists of two distinct zones, one overlying the papillae of the supporting connective tissue (PBL) and the other covering the interpapillary zone (IBL). Current analysis of the cell division and regeneration in the oesophageal epithelium combined with immunohistochemical studies [85] for proliferating cells have demonstrated that basement membrane components in the oesophageal interpapillary basal layer (IBL) could be a source of stem cells. Oesophageal stem cells demonstrate several unusual properties. In the IBL cell division is asymmetrical, occurring at right angles to the underlying basement membrane. This yields one daughter cell remaining in the basal layer (a putative stem cell) and one that enters a zone of high proliferative activity (transit amplifying cell).[86] In the PBL, mitoses were more frequent and predominantly symmetrical. Possibly stem cells located in the IBL give rise to differentiating daughter cells through asymmetric divisions in response to cues from the underlying basement membrane.Contrary to the

81 Ramon-Cueto A, Cordero MI, Santos-Benito FF, Avila J. Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfatory ensheating glia. Neuron 2000: 25, 425-35.

82 Roisen FJ, Klueber KM, Lu CL, et al. Adult human olfactory stem cells. Brain Res 2001;890:11-22.

83 Salck JM. Stem Cells in epithelial Tissues. Science 2000; 287: 1431-3.

84 Taylor G, Lehrer MS, Jensen PJ, Sun TT, and Lavker RM. Involvement of follicular stem cells in forming not only the follicle but also the epidermis. Cell 2000;102:451-61.

85 Seery JP and Watt FM. Asymmetric cell-divisions define the architecture of the human oesophageal epithelium. Curr Biol 2000;19:1447-50.

86 Seery P. Stem cells of the oesophageal epithelium. Journal of Cell Science 2002;115:1783-9.

behaviour of the epidermal stem cells that proliferate independently of interactions with their underlying stroma,[87] the basement membrane of the oesophageal epithelium plays a central role in the orientation of cell division. When oesophageal keratocytes are cultured in vitro on denuded acellular dermis the orientation of the cells is arbitrary and the epithelium formed is featureless. When intact basement membrane is present the orientation of cell division is generally symmetrical and the epithelium formed resembles the in vivo tissue.[88] It is not known whether signals from the surrounding tissue can alter the balance between stem cell and transit amplifying cell production. Some authors suggest that tubuloalveolar glands, present in the submucosa along the length of the oesophagus could also be a source of stem cells that are involved in the reconstitution of the epithelium after mucosal injury.[89] More basic information about the behaviour of oesophageal stem cells is required. Not every cell in the IBL seems to be a stem cell and studies of the expression of cytokeratin mRNA's in normal human oesophageal epithelium show further subdivisions of cell function in this region.[90]

Stem cells from fat

Adipose tissue seems to be a relevant source of stem cells. Researchers at the University of California at Los Angeles separated stem cells from fat removed from patients undergoing liposuction and coaxed the stem cells to turn into four different types of cells. These cells have been found in great numbers in fat obtained from liposuction treatments. Human fat stem cells could be expanded and maintained in culture for extended periods. Depending on the culture conditions, they might have the ability to differentiate into fat, cartilage, muscle, bone and other connective tissues.[91] These results suggest the possibility of repairing cartilage injury using the patient' s own fat cells.

Current experiments showed that adult fat stem cells can also be transformed into cells of a totally different lineage, such as neurons that can be used to treat injuries such as stroke and spinal cord injuries.[92]

87 Jones PH, Harper S, and Watt FM. Separation of human epidermal stem cells from transit amplifying cells on the basis of differences in integrin function and expression. Cell 1995;73:713-24.

88 Seery JP and Watt FM. Asymmetric cell-divisions define the architecture of the human oesophageal epithelium. Curr Biol 2000;19:1447-50.

89 Gullie P, Keeling P, Byrne PJ, West AB, and Hennessy TP. Experimental columnar metaplasia in the canine oesophagus. Br Journ Srug 1998;75:113-5.

90 Viaene AI and Baert JH. Expression of cytokeratin mRNAs in normal human esopaheal epithelium. Anat Record 1995 ;241:88-9.

91 Zuk PA, Zhu M, Mizuno H et al. Multilineage Cells from Human Adipose Tissue: Implications for Cell-Based Therapies. Tissue Eng 2001;7:211-28.

92 Safford KM, Hicok KC, Safford D, Halvorsen Y-D C, Wilkinson WO, Gimble JM, Rice ME. Neurogenic differentiation of murine and human adipose-derived stromal cells. J. Biochemical and Biophysical research Communications 2002; 294: 371-9.

Stem cells of the eye

That stem cells are present in the eye of mammalians is known for more than 20 years. To date, stem cells have been found in the limbal zone and in the retina. Autologous and heterologous limbal stem cell transplants have successfully restored the vision in patients with Stevens-Johnson syndrome and with blindness caused by chemical factors.

A team at Emory University School of Medicine has shown that implanting retinal cells into the brains of people with advanced Parkinson's disease can improve motor function by almost half, according to a follow-up study of six patients. The patients have been followed for over a year and they were found to be improved, on average, nearly 50 per cent in motor function. The retinal cells used were taken from deceased donors and grown in the lab.[93]

Although the number of stem cells in the retina seems to be very limited, the addition of growth factors could make it possible to obtain clinically significant amounts of these cells.[94]

Umbilical cord

One of the most promising sources of pluripotent stem cells is the blood from human umbilical cord and placenta. Like bone marrow, cord blood is enriched with stem cells: approximately 4 million cells can be obtained from 200 ml blood. These cells can be maintained for a long time in vitro without reduction of their therapeutic potential for transplants and genetic therapies.

Cord blood stem cells appear to have greater proliferation capacity than adult bone marrow stem cells and are less likely to cause graft-versus-host disease. The differentiated cells produced by cord blood, peripheral blood and bone marrow stem cells do not show qualitative differences. Umbilical cord blood human stem cell transplants have been successfully used in treatment of children with Fanconi anemia.[95] These cells have also shown anti tumour activity against leukemia cells and breast cancer cells in mice.[96]

Placenta

Placenta seems to offer a new rich source of stem cells that can be used for different replacement therapies. By removing all the blood from a placenta and keeping it on life-support for a few days under special conditions it is possible to extract stem cells from the tissue in quantities roughly 10 times those that could be taken from an umbilical cord. These cells can develop into nerve,

93 Results presented April 18 at the Annual conference of the American Academy of Neurology in Denver and reported in:. Note: There are no clinical treatments for Parkinson's based on cloning or embryonic stem cells. NewScientist , April 18, 2002;www.newscientist.com/nes/.

94 Tropepe V, Coles BLK, Chiasson BJ, Horsfort DJ, Elia AJ, McInnes R, Van der Kooy D. Retinal stem cells in the adult mammalian eye. Science 2000; 287: 2032-6.

95 Laughlin MJ. Umbilical cord blood for allogenic transplantation in children and adults. Bone Marrow transplant 2001;27:1-6.

96 Joshi SS, Tarantolo SR, Kuszynski CA, and Kessinger A. Antitumour therapeutic potential of activated human umbilical cord blood cells against leukemia and breast cancer. Clin Cancer res 2000;6:4351-8.

blood, skin and muscle cells, and perhaps into bone and cartilage. In addition placental stem cells are unlikely to be rejected by the recipient's immune system.

MAPC cells

In recent research, a type of adult stem cell has been isolated that could be induced to develop into every single tissue in the body, the so-called MAPC cell or 'multipotent adult progenitor cell'.[97] MAPC cells have been tracked down in adult bone marrow of mice, rats and human and appear to be able to transform into most, if not all, somatic tissues

Experiments in which isolated MAPC cells were injected into 3.5-day-old blastocyst of mice revealed that a single MAPC differentiates into cells with morphologic, phenotypic and functional characte-ristics of cells representing the three germ layers. Although some MAPC derived cells were found in the gonads of the mouse, it is not yet known whether MAPCs contribute to the germ line. For unknown reasons, MAPCs had a 66% failure in contributing to the development of the mouse. Possibly this failure may be due to technical problems with injection of a single cell.

MAPCs infused intravenously in post-natal animals engraft and differentiate into lung, liver, intestine, gut, blood, brain cells, and other organ cells. In response to local cues, MAPCs may migrate spontaneously to damaged tissues where they are needed. This is supported by the finding that no cell turnover is seen in skeletal or cardiac muscle, tissues that were not injured, indicating the MAPC's did not differentiate into cell types of these tissues.

Although the work is still at an early stage, these findings confirm the evidence that adult cells may be almost as versatile as ES cells. The MAPCs could be grown in culture over 120 generations without losing their capacity to differentiate into other tissues. This is more than twice the number previously thought possible for adult stem cells. In contrast with ES cells, MAPCs do not appear to develop tumours when injected into animals. Furthermore, the cells could be isolated from the patient avoiding possible rejection by the immune system. Defective genes in a patient's own MAPCs could possibly be corrected by gene therapy. In addition, a combination of MAPC and gene therapy could also be used to correct genetic or inherited diseases. MAPC could be isolated from a patient and a correct gene could be inserted into their DNA. After growing sufficient quantities of the modified cells, they could be re-injected into a deficient organ. Hopefully this may give rise to healthy cells of that organ.

The results obtained so far appear to confirm that in the adult organism undifferentiated cells remain as a possible mechanism for repairing tissue damage. When this mechanism appears to fail in repairing tissue damage related to some disease, tissue engineering using MAPC or other stem cells could be used to treat the disease. So, irrespective of their origin, MAPCs hold great promise for the treatment of degenerative or inherited diseases. Now,

97 Jiang Y, Jahagirdar BN, Reinhardts RL, Schwartz RE, Keene CD, Ortiz-González XR, Reyes M, Lenvik T, Lund T, Blackstad M, Du J, Aldrich S, Lisberg A, Low WC, Largaespada DA and Verfaille CM. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002;417, published on line June 20, 2002;doi: 10.1038/nature00870.

the next step to be done is to determine the way to direct the cells to a predetermined body part and make them function there.

Adult tumour cells

Cells derivated from an adult tumour, a teratocarcinoma[98], are shown to be able to differentiate into neurons. These cells have been successfully used in treatment of Pakinson[99] and stroke patients.[100]

Disadvantages of adult stem cells

While treatment with adult stem cells holds real promises, there are some significant limitations to what may or may not be accomplished with them.

The most important disadvantage is that adult stem cells are often present in only minute quantities dispersed throughout tissues of the organism and are difficult to identify, isolate, and purify. Any attempt to use the patient's own stem cells requires the isolation of stem cells from the patient and their cultivation in vitro in sufficient quantities for treatment. This would mean that for some acute, rapidly progressing disorders there may not be sufficient time to grow enough cells for treatment.

Furthermore, when diseases are caused by injury or foreign agents such as toxins or bacteria, these would probably also affect adult and embryonic stem cells that are transferred into the patient as long as the agents would still be in the patient. A more lasting effect could then be expected only after removal of those agents.

Adult stem cells appear to depend on their local environment for their behaviour. For instance, hematopoietic stem cells are constantly being generated in the bone marrow where they differentiate into mature types of blood cells. Stem cells in the small intestine are stationary and are physically separated from the mature cell types they produce. Gut epithelial stem cells divide often but remain part of the stationary group of cells they generate.

Another important limiting factor is that stem cells do not have the capacity to reproduce in an unspecialised state in the laboratory for long periods. Their potential and numbers may decrease with age. As a result, insufficient numbers of cells are available for transplantation. However substantial progress has already been made towards increasing the proliferation rate of cells in culture. Furthermore, the treatment of an individual patient using cells derived from his own tissue would not require the large numbers of cells needed to treat large populations of patients.

98 Teratocarcinoma is sometimes called " embrional carcinoma" because it mimics some of the characteristics of embryonic cells

99 Lacovitt L. Differentiation of human dopamine neurons from an embryonic carcinomal stem cells line. Brain Resp 2001; 912 (1): 99-104.

100 Kondziolka D, Wechsler L, Goldstein S, Meltzer C, Thulborn KR, Gebel J, Jannetta P, DeCesare S, Elder EM, McGrogan M, Reitman MA, Bynum L. Transplantation of cultured human neuronal cells for patients with stroke. Neurology 2000; 55: 565-9.

As indicated before, in disorders that are caused by a genetic defect, the genetic error would likely be present in the patient's stem cells, making cells from such a patient inappropriate for transplantation. In addition they may contain more DNA abnormalities caused by exposure to daily living, including light, toxins and errors made during DNA replication. But the vast majority of diseases due to genetic factors occur relatively late in the patient's life. This suggests that such disorders would take years to re-emerge in newly generated replacement cells.

In addition to these limitations, research on the early stages of cell specialisation may not be possible with adult stem cells since they are further along the specialisation pathway than are pluripotent stem cells.

2.5. Comparison between ES and adult stem cells

Actually, it is difficult adequately to compare stem cells obtained from embryonic, foetal and adult sources. These stem cells not only differ with respect to the source from which they are recovered, but also with respect to their growth characteristics in vitro and in their behaviour in vivo. From a medical point of view, in order to determine the advantages and disadvantages of stem cells from different sources, research has to be carried out in which the various types of stem cells are carefully compared with respect to characteristics and possibilities. To date most of the experiments in different laboratories are performed with differing conditions and cell lines. There have been very few studies that side-by-side have tested stem cells from different sources. It may be that stem cells from differing sources prove better for differing applications.

The most distinguishing feature of ES cells and adult stem cells is their source. Although adult stem cells are difficult to characterise and the origin of stem cells in the mature tissue is not yet known, most scientists agree that they exist in many tissues of the human body in vivo. In contrast, it is not clear that ES cells and EG cells as such exist in the embryo. They are grown in culture after they are harvested from the human blastocysts or the gonadal ridge tissue of the foetus respectively.

Stem cells from different sources do not appear to have the same ability to proliferate in culture and to retain the capacity to differentiate into functionally specialised cells. ES cells may have an unlimited ability to proliferate in vitro and can be grown in their undifferentiated state, thereby giving rise to several hundreds of population doublings. EG cells can be maintained for only 70 to 80 population doublings. Until recently, adult stem cells were thought to be difficult to grow in the laboratory without losing differentiation potential. However, experiments with oligodendrocyte precursor cells have shown that the regenerating potential of adult stem cells may be greater than believed earlier and, perhaps, than the potential of embryonic stem cells.[101] Growth and differentiation of adult stem cells are much easier to control than ES cells, both in vitro and in vivo. Adult stem cells show a higher degree of genomic stability

101 Tang DG, Tokumoto YM, Apperly JA, Lloyd AC, and Raff MC. Lack of replicative senescence in cultured rat oligodendrocyte precursor cells. Science 2001;291:868-71.

than ES cells. When undifferentiated human ES cells are injected into immune-compromised mice, they can generate teratomas containing differentiated cell types. This property has not been observed in human EG and adult stem cells.

The main difference between ES, EG and adult stem cells is thought to be in the number of specialised cell types they can produce. ES and EG cells are believed to be pluripotent. Although ES cells appear to have a broader differentiation potential, both ES cells and EG cells generate in vitro embryonic bodies that consist of cell types from the three germ lagers. With respect tot adult stem cells scientists assumed that they were programmed to produce specific -perhaps 3 or 4- tissue types only. However, one of the most surprising discoveries of recent years is that, in contrast to earlier established opinion, under experimental conditions adult stem cells are able to produce cell types other than those produced in vivo.

Adult stem cells have been used directly after isolation or after expansion in culture. When transplanted into a patient they simply differentiate according to cues from surrounding tissues. ES cells, on the other hand, require extensive treatments and even genetic modification, before they can be safely used.

It appears to require less work to transform adult stem cells into specialised cells for transplantation than using ES cells.[102] Moreover, it seems easier to get pure cell populations from adult stem cells than from either human or mouse ES cells.

A significant advantage of adult stem cells is that the use of a patient's owns cells would circumvent one of the major obstacles posed by the use of embryonic stem cells, namely the infection and rejection dangers that could arise when tissue taken from one individual is transplanted in another, the patient.

3 OTHER METHODS FOR OBTAINING STEM CELLS

3.1. Somatic Cell Nuclear Transfer and its problems

Human embryonic stem cell preparations could potentially be produced by using somatic cell nuclear transfer (SNCT) to produce a cloned human embryo from which in the blastocyst stage stem cells could be isolated. In studies with animals using SCNT, researchers take a normal animal egg cell and remove the nucleus. A somatic cell is placed next to the enucleated egg cell and the two cells are fused. Cloning experiments with animals (of which sheep Dolly was the first) show that the resulting fused cell and its immediate descendants in principal have the full potential of developing into an entire animal, and hence are totipotent. If this could and would be done with human cells, pluripotent ES cells could be harvested from the artificially created human embryo in the blastocyst stage.

102 Marshall E. The business of stem cells. Science 2000 ;25:1418-9.

Although so far the real benefits of such research are unclear, many researchers believe it will yield very useful and important knowledge pointing towards new therapies and offering one of several possible routes to avoid the immune rejection problem. Stem cells obtained from a cloned embryo could be genetically virtually identical to the individual from which the somatic cell nucleus was obtained and hence would not pose the risk of tissue rejection that occurs after transplantation of cells from other individuals. (This process is also called 'therapeutic cloning', but 'research cloning' is a better term). This means that the patient does not need to be exposed to immune-suppressing drugs that also have toxic effects.

Some animal experimental results in this field are quite encouraging. They also demonstrate that the risk of immune rejection is not completely absent by 'research cloning'. Proteins encoded by mitochondrial genes (which come from the egg cell and are therefore different from the corresponding genes in the nucleus donor and in the clone embryo) can stimulate the immune system. In addition, stem cells obtained by cloning may be useless for treating genetic diseases such as juvenile diabetes, since these cells will have the same genetic defect that caused the problem in the first place.

At least seven species of mammals have been cloned to produce live births.[103] However, 90 percent of the cloned animals fail to develop normally and abort spontaneously in utero. Moreover, the live-born cloned animals present high rates of deformity and disability, both at birth and later on. A recent survey of this kind of research on mice concludes that the low efficiency of 'therapeutic cloning' is so low that "in its present form, the concept is unlikely to become widespread in clinical practice".[104] Some scientists attribute these failures to genetic abnormalities due to damage or complete failure of epigenetic reprogramming of the somatic cell nucleus caused by its isolation from the donor cell and its introduction into the egg cell. Attempts to clone primates using adult cell nuclei have not been able to go beyond the 6 cell-embryo stages, in which stem cells are not yet formed. This is possibly due to the damage caused by the removal of the nucleus from the egg cell. Further research has demonstrated that the cells in primate clones do not form distinct nuclei that contain all the chromosomes. It has also been found that the gene Oct-4, essential for the differentiation of the blastocyst, switches on at the wrong time or place in the cloned embryos, rendering the clone unable to undergo the early stages of implantation.[105]

For scientists more interested in the development of the embryo and of stem cells, SCNT research may enhance our understanding of reprogramming faulty human genes rather than making stem cells for transplantation purposes.

103 Shin T, et al. A cat cloned by nuclear transplantation. Nature 1998;415:859.

104 Published online before print August 29, 2003, Proc Natl Acad Sci USA, 10.1073/pnas.1934141100.

105 Boiani M, Eckardt S, Scholer HR and McLaughlin KJ. Oct4 distribution and level in mouse clones: consequences for pluripotency. Genes and Development 2002;16:1209-19.

Cloning of hybrid embryos

An alternative for research cloning without making human embryos is to produce hybrid embryos by injecting human somatic nuclei into egg cells of animals. Extracting eggs from women is difficult and potentially dangerous.

Scientists have succeeded in injected human nuclei into a cow egg cell that subsequently divided a few times. Chinese researchers have fused a human fibroblast with a rabbit egg cell and have grown the resulting 'embryo' to the blastocyst stage. So far it has not been possible to grow such a hybrid beyond the blastocyst stage and it is doubtful whether that will be possible at all. This technique raises the interesting question about the biological and ethical status of these artificially made hybrid embryos.

We will come back to this in chapter 3.

3.2. Parthenogenesis

Parthenogenesis could potentially be a way to obtain pluripotent human embryonic stem cells without destroying viable embryos. By this method, unfertilised egg cells are induced to divide by exposure to certain stimuli, such as, intense heat or cold, vacuum pressure, noxious chemicals, or electric shocks. The egg cell thus activated undergoes repeated cell cleavages and develops as if it had been fertilised, giving rise to blastocysts.

Unlike normal embryos, which contain genetic material from the father and the mother, the parthenote contains genetic material only from the mother. With the exception of one reported case of a live born rabbit[106] no parthenogenetic mammal has survived beyond the embryonic stage. Depending on the stage in which the meiosis is suppressed the parthenote may be haploid, diploid, polyploid or hapodiploid mosaic.[107] The parthenote is not an exact genetic duplicate or clone of its mother because of the genetic shuffling that occurs in the cross over of sisters chromosomes during the meiosis.

Because of the absence of paternal factors vital to normal embryonic development,[108] the human parthenote cannot develop into a normal foetus. Most of the cultured human parthenogenetic embryos arrest by the third cell division when the embryo has reached the 8-cell or morula stage in which stem cells are not yet present. However, recent experiments with primates have succeeded in isolating stem cells from a primate embryo derived through the technique of parthenogenesis. These stem cells were made to differentiate into a large variety of specialised cell types including heart muscle, smooth muscle, beating ciliated epithelial cells and dopamine producing neurons.[109] Similar

106 Cit. from Cheshire W M. The ethics of human parthenogenesis. Christian Medical Association 2002. Original publication: Pincus G, Shapiro H. Further studies on the parthenogenetic activation of rabbit eggs. Proc Natl Acad Sci 1940; 26: 163-165. Since this reported finding from over 60 years ago apparently has not been repeated one may wonder what really happened then.

107 Rougier N, Werb Z. Parthenogenesis in mammals. Mol Reprod Devel 2001;59:468-74.

108 These factors are the paternal imprinting, the paternal centrosoma and the normal paternal genes that can silence the defective lethal genes from the mother

109 Cibelli JB, Grant KA, Chapman KB, Cunnif K, Worst T, Green HL, et al. Parthenogenetic stem cells in nonhuman primates. Science 2002;295:819.

results have been obtained with stem cells from parthenogenetic mouse embryos.[110] Actually, it is not known whether stable stem cell lines could be cultured from human parthenotes.

The same problems that render a parthenote defective could affect the potential therapeutic efficacy and safety of its progeny stem cells, which could likewise be genetically defective. The lack of paternal imprinting might affect the maturation, function, and stability of the parthenogenetic stem cells. Secondly, parthenogenesis could lead to altered levels of gene expression that may increase the risk of developing into malign tumours. Stem cells from parthenogenetic primates developed into teratomas when injected into mice. Another disadvantage of the parthenogenetic therapy is that it might benefit only women since the parthenogenetically derived cell would be immunologically compatible only with the egg donor.

3.3. Gene therapy

The first experiments applying gene therapy for treatment of human diseases go back to 1989. Initially this research focused on cancers, aids and disorders due to only one abnormal gene such as cystic fibrosis, Fanconi anemia, Fabry disease, Gaucher's disease and leukocyte adherence deficiency. Currently, scientists are trying to apply it to chronic diseases that involve more than one abnormal gene. Gene therapy is based on the use of genetic engineering to provide a copy of a normal gene that can remedy the function of an abnormal gene.

One strategy for delivering therapeutic transgenes into a patient includes the use of stem cells. In this procedure stem cells are isolated from the patient, and the therapeutic transgene is introduced into them in vitro through a delivery vehicle such as a virus. The treated stem cells are allowed to grow in the laboratory, the cells are tested on the presence of the transgene and the genetically modified stem cells are injected back into the patient. To date only adult stem cells, specifically hematopoietic stem cells removed from the peripheral blood and bone marrow of adults or the umbilical cord blood have been used in gene therapy. Other types of adult stem cells such as muscle, bone and neural stem cells, are being studied as gene-delivery-vehicle candidates.

The principal reason for using stem cells for cell-based gene therapy is that their capacity of self-renewal may reduce or eliminate the need for repeated administrations of the gene therapy. Hematopoietic stem cells are of particular interest because of their ability to migrate to different places in the body such as bone marrow, liver, spleen, and lymph nodes. This suggests that hematopoietic stem cell-based therapy might be used not only in diseases related to the blood system, but also in liver diseases and metabolic disorders such as Gaucher's disease.

110 Feng Y, Hall JL. Production of neurons from stem cells derived from parthenogenetic mouse embryos. Fertility and Sterility 2001;76(suppl 1):S32

Since muscle tissue is supplied with nerves and the circulatory system, myoblast could possibly be used to treat muscle disorders, such as muscular dystrophy, and also non-muscle disorders such as neurodegenerative diseases, hormone deficiencies, hemophilia and cancers. Experiments in mice have shown that myoblast-mediated gene therapy could be promising in treating liver and spleen abnormalities, anaemia[111] and amyotrophic lateral sclerosis, a progressive degeneration of the brain and spinal cord nerves that control muscle activity.[112]

Neural stem cells have been tested as vehicles for cell-based therapies on gliomas in mice. Two weeks after the injection of genetically modified cells, the tumours had shrunk by 80%.[113]

A Japanese research team demonstrated that delayed delivery of gene therapy can provide significant recovery from Parkinson's symptoms. Four weeks after inducing Parkinson's-like dama-ge in their brains, rats were given an injection of a gene vector which produced a growth protein call "glial cell line-derived neurotrophic factor" (GDNF). The animals showed remarkably higher levels of dopamine secretion and significant behavioural recovery, even up to 20 weeks following the injection.[114] Treatment with three gene therapy vectors has also shown a important recovery in Parkinson's monkeys. The treatment resulted in improvement in manual dexterity and restoration of motor functions, with the behavioural recovery persisting for over 10 months in one case. The scientists say that this triple gene therapy method may offer a potential herapeutic strategy for Parkinson's disease.[115]

Although ES cells have a longer life span and proliferation capacity than adult stem cells they do not seem to be potential candidates for gene therapy. Because ES cells can give rise to teratomas when injected in a patient, adult stem cells that give rise to a limited number of cell types may be better candidates for cell-based gene therapy.

111 Ozawa CR, Springer ML, and Blau HM. A novel means of drug delivery: myoblast-mediated gene therapy and regulatable retroviral vectors. Annu Rev Pharmacol Toxicol 2000;40:295-317

112 Mohajeri MH, Figlewicz DA, and Bohn MC. Intramuscular grafts of myoblasts genetically modified to secrete glial cell line-derived neurotrophic factor prevent motoneuron loss and disease progression in a mouse model of familiar amyotrophic lateral sclerosis. Hum Gene Ther 1999;10:1853-66.

113 Aboody KS, Brown A, Rainov NG, Bower KA, Liu S, Yang W, Small JE, Herrlinger U, Ourednik V, Black PM, Breakefield XO, and Snyder EY. Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas. Proc Natl Acad Sci USA 2000;97:12846-51.

114 Wang L, Muramatsu S, Lu Y, Ikeguchi K, Fujimoto K, Okada T, Mizukami H, Hanazono Y, Kume A, Urano F, Ichinose H, Nagatsu T, Nakano I, Ozawa K. Delayed delivery of AAV-GDNF prevents nigral neurodegeneration and promotes functional recovery in a rat model of Parkinson's disease. Gene Therapy 2002; 9(6):381-9.

115 Muramatsu S, Fujimoto K, Ikeguchi K, Shizuma N, Kawasaki K, Ono F, Shen Y, Wang L, Mizukami H, Kume A, Matsumura M, Nagatsu I, Urano F, Ichinose H, Nagatsu T, Terao K, Nakano I, Ozawa K. Behavioral recovery in a primate model of Parkinson's disease by triple transduction of striatal cells with adeno-associated viral vectors expressing dopamine-synthesizing enzymes. Human Gene Therapy 2002;13:345-54.

3.4. Genetic reprogramming of adult cells

One approach to produce ES-like stem cells without the use of embryos is to reprogram adult cells in order to revert them into stem cells that can be grown and coaxed to differentiate into different types of cells needed for transplantation purposes.

A method for genetic reprogramming is fusing a somatic cell of a patient with an embryonic stem cell. The adult cells appear to retrograde to a less differentiated state. Cow skin cells have been converted to multipotent stem cells that were induced to differentiate into cardiac muscle cells.[116]

Another method for genetic reprogramming of adult cells is the transfer of the cytoplasm from an egg cell into a mature adult cell. The cytoplasm seems to induce the specialised adult cell to retrograde to a less differentiated state.

3.5. Other methods

A recent breakthrough in repair therapy concerns a technique that transforms one type of specialised cells into other cell types of the body. By immersing human skin cells in extracts of immune cells or nerve cells, Collas succeeded in inducing them to behave in vitro as immune system cells or nerve cells, respectively. Although the skin cells were not completely transformed into other cell types, this method would allow a patient's own skin cells to be turned into the cells that are needed to treat a particular disease without using therapeutic cloning and without needing women's eggs.

This technique by Collas is based on the fact that all the body's cells have the same genes, but different genes are active in different types of cells. Transferring skin cells previously treated to increase their potential to take up proteins from the environment, to a medium containing extracts of immune cells results in a migration of proteins that switch on particular genes of the skin cells. Certain genes that normally are active in immune cells became active in these skin cells, while some genes active in skin cells became inactive.[117]

These results so far only pertain to laboratory experiments and it is not yet known whether this technique would function in vivo. Nonetheless, they are an indication that a variety of tissues could be generated from adult specialised cells without reverting them to the embryonic state by research cloning.

One approach to tissue regeneration that does not rely on stem cells at all, but on somatic cell gene therapy, is already used as an experimental treatment. A gene that controls production of growth factors can be injected into a patient's own cells, resulting in the development of new blood vessels. In early trials, this type of therapy saved the legs of patients who would otherwise have undergone amputation. Although there are some difficulties in getting these growth factors to the injury site, new delivery methods are developed to target

116 James. Communication on the Congress of the British Society of Fertility. February 23, 2002.

117 Håkelien A, Landsverk HB, Robl JM, Skålhegg BS, Collas P. Reprogramming fibroblasts to express T-cell functions using cell extracts. Nature Biotechnology 2002;20(5):460-6.

particular cell types to different places in the body[118] It was reported in January 1999 that the technique has generated new blood vessels in a human heart and improved the condition of 19 out of 20 patients with blocked cardiac blood vessels. Injection of a gene vector which produces a growth protein call "glial cell line derived neurotrophic factor" into the brains of rats with induced Parkinson's damage showed an improvement of the levels of dopamine secretion and significant behavorial recovery, even up to 20 weeks following the injection.[119]

4 CONCLUSIONS

The proliferate capacity of embryonic and adult stem cells combined with their ability to specialise, makes stem cells unique for potential therapeutic applications to repair or replace cells or tissues damaged or destroyed by degenerative diseases. Though both types of stem cells hold promises for treatment of patients, they also differ in important ways. While there are many theoretical reasons why embryonic stem cells may be more suitable for transplantation therapy due to their capacity to give rise to every type of cell, so far in practice there is no evidence that any ES cell can develop

into all types.[120] Despite the serious limitations to the potential usefulness of ES cells, the argument in favor of this research would be considerably stronger if there were no viable alternatives. However, there are alternatives. In recent years, important advances have been made in research on human adult stem cells. The results obtained so far suggest that these multipotent cells are present in more human tissues than previously thought and that they are capable of developing into almost all the specialised cells of the body. The latest breakthroughs of adult stem cells demonstrating unexpected capacity of transformation and particularly the discovery of MACP cells, indicate that these cells are as versatile as ES cells. In many areas even the most successful results with embryonic stem cells are eclipsed by adult stem cells in the treatment of disease. Because of the risk that ES and EG cells, in contrast to adult stem cells, develop into teratomas when injected into histocompatible animals, it seems preferable to use adult stem cells for the treatment of patients. The use of an individual's own stem cells offers advantages over other sources because it reduces the risk of infection and because they are unlikely to be rejected by the patient's immune system.

The objection that adult stem cells are not able to generate the full spectrum of cells found in the body may in fact be a scientific advantage. Since ES cells have the potential to develop into any other cell type, ES cells must make choices that progressively restrict the possibilities of what it can become. The

118 Jackson CA, Peduzzi JD, Novak M, Morrow CD. Repetitive intrathecal injections of polivirus replicons result in gene expression in neurons of the central nervous system without parthenogenesis. Human Gene Therapy 2001;12:1827-41.

119 Rosengart TK, Lee LY, Patel SR, et al. Angiogenesis gene therapy: Phase I assessment of direct intramyocardial administration of an adenoviral vector expressing VEGF 121 cDNA to individuals with clinically significant severe coronary artery disease. Circulation 1999;100:468-74.

120 Yamashita J, Itoh H, Hirashima M, Ogawa M, Nishikawa S, Yurugi T, Naito M, Nakao K, and Nishikawa S. Flk 1-positive cells derived from embryonic stem cells serve as vascular progenitors. Nature 2000;408:92-6.

greater the number of steps required to archieve specialisation, the greater the scientific challenge to reproduce those steps in tissue culture. The fact that adult stem cells have a limited potential of differentiation may indicate that they have proceeded at least part of the pathway towards their final state, thereby reducing the number of steps scientist are required to replicate in culture. In addition, the restriction in developmental potential of adult stem cells would not limit their therapeutic potential for treatment. Patients rarely need a full body replacement. The totality of different adult stem cells allow scientists to obtain almost all the cells they need for specific treatments.

It is important to note that the use of adult stem cells would avoid the limitations and ethical concerns pertaining to stem cells from other sources. Furthermore, until now only adult human stem cells are understood well enough and can reliably be differentiated into specific tissue types.

At this time, it is very difficult to predict the future of stem cell applications since stem cell research is only in its infancy. There is a long way to go in basic research before cells from the different sources can be used for clinical applications in patients. The latest advances obtained with adult stem cells open a wide field of treatment of degenerative diseases that does not depend upon destructive embryo research and seems to indicate that ES cells are not essential for medical progress. In addition, research on adult stem cells can be done with a minimum of intervention in order to minimise side effects and cost. Possible approaches are to stimulate cells to regenerate in situ or to regenerate organs in culture by seeding adult stem cells isolated from the patient with material from the type of tissue one wants to generate. This all suggests that there are good reasons to continue the research with stem cells derived from adult tissue and to pursue their potential for treatment of human disease.

The creation of embryos by somatic cell nuclear transfer may be premature since there is a wide field of research to be carried out with alternative sources of human stem cells. Furthermore, if we could understand how egg cytoplasm can reprogram a nucleus perhaps we could reprogram the patient’s somatic nucleus into stem cells without any need of eggs of embryos.

3

Ethics of stem cell research

Dr Elisa Garcia and Dr Henk Jochemsen

1 INTRODUCTION

What is ethics?

We all know that human beings sometimes behave in a way that is felt to be bad, evil, unjust. In other words, people have moral experience. The notion that it matters how we act and behave is typical for human beings. A question constantly facing human beings and communities is: how should we behave, what is a good way of living? The answer to this question depends on a concept of the good (in a moral sense) life, which in turn depends on the view one has on the meaning of human life. The systematic study of these questions and of the answers is the task of ethics as a scientific discipline. The word ethics is derived from the Greek ethos (character), which means habit or custom. The related word morals (morality) is from the Latin word mos, which means custom in the sense of natural inclination to act with an intention, i.e., with a direction to an end.

These two terms express how individuals choose to interact with one another. In philosophy, ethics studies what is good for the individual and for society and establishes the nature of duties that people owe themselves and one another. Whether an act or a certain behaviour are considered morally good or bad depends on what is considered the true end of the human being.

Many existing concepts of ethics, while valuable and informative, are incomplete. Utilitarians, deontologists, casuists, communitarians, contractarians, and ethicists of other persuasions appeal to different models of ethical reasoning.

Utilitarians follow a consequentialist type of ethics, judging the rightness or wrongness of a given action exclusively by its consequences. To be morally right an action must provide the most utility (defined in terms of happiness, or satisfaction) for the greatest number of persons[121]. The utilitarian approach can be critiqued by arguing that it is almost impossible to quantify happiness and satisfaction. The denial of the distinction between the intention of the acting subject and his acts or omissions is also controversial.

Deontological (duty) theories are based on the Kantian approach which affirms that only duty should motivate morally adequate actions. An action done from duty has its moral worth in the maxim in accordance with which it is decided upon[122]. Deontological-Kantian theories are not concerned about the consequences of action, tending to defend absolutist positions.

Communitarian ethics rejects the idea of an isolated, knowledgeable subject arguing that the interests and values of the community determine the morality of the action. For them, any moral theory is determined by the historical and social context of the community. The moral principles and values cannot be considered as simple human conventions. Because morality is an essential aspect of the nature of mankind, the moral principles and values are objective and valid for each person. That ethics is for everybody does not mean that

121 Mill JS. Utilitarianism. Hackett Pub Co, 2002; 2

122 Kant I. Critique of Practical Reason Garland. New York, 1976: 67-8

being ethical is the same as following the standards of behaviour our society accepts. The law and beliefs accepted by most people could deviate from what is ethically justified. An entire society can become ethically corrupt. Furthermore, the lack of social consensus on many issues makes it impossible to identify the ethically good with whatever society accepts. An important task of ethics is the continuous effort of studying our moral beliefs of people and society to ensure that they are in agreement with human dignity and human well-being.

Religious ethics is based on the particular religious beliefs of the acting subject or ethicist. Religious traditions form a strong basis for fundamental beliefs and values and religion sets high ethical standards and provides intense motivations for ethical behaviour. Yet, we cannot identify ethics with religion. Religion is much more than ethics and in addition, world views can provide a basis for ethics. This does not rule out that different religions or world views sometimes lead to similar fundamental ethical views on certain areas.

Some people tend to equate ethics to feelings. But a person following his feelings may recoil from doing what is right. Though feelings certainly have a role in ethics – moral experience often indicates that certain important values are at stake - because of their very personal and fluctuating character they cannot tell us what is right or wrong. In fact, they frequently deviate from what is ethically good. For instance, think of feelings of rage and revenge. It is one's reason that determines appropriate actions.

Ethics involves arriving at moral standards that regulate right and wrong behaviour. But ethics does not only formulate rules. It deals with human acts in so far as they are free and voluntary. It provides us with the necessary knowledge to freely determine how we must behave in a concrete situation in order to act in a morally correct way. Ethics does not only help us to determine which actions are allowed and which not, but what is the right thing to do in a given situation in order to act according to our dignity as persons. The latter is the viewpoint of the virtue theory. This theory differs from rule-oriented approaches in that it places less emphasis on learning and following rules, stressing the importance of developing good habits and conduct. The central question of ethics is "what is the good life?" and the answer given by the virtue theory takes the form of "the virtuous life".[123] A central point in this theory is the idea that the virtuous person also has the capacity to discern in a concrete situation which is the ethically good way to act and to act accordingly.

Ethics and world view

We indicated above that ethics deals not just with individual human actions. It also pertains to an understanding of the good life, of humans flourishing amidst many forces that often frustrate such flourishing, like disease, suffering and death. The human being has always tried to resist such threats to his personal life, relations and community. Technology is obviously a powerful weapon in this battle. At the same time it is recognised that technology can also become a new threat precisely because of its power. Scientific and technological

123 Aristotle. The Nichomachean Ethics. [trans. Ross WD] Oxford (UK): Oxford University Press, 1989

advances have made possible the study and manipulation of the human being in its bodily existence at the molecular and cellular level, but have also released the spectre of interventions that would violate human dignity instead of serving it.[124] Awareness of this provides a background for many debates in society at large and in politics about new technological developments, not least in the fields of biomedicine and biotechnology, and the establishment of ethical committees like the President's Council on Bioethics in the USA and the European Group on ethics in science and new technologies to the European Commission in Europe.

To clarify the ethical debate and underline its fundamental character we find it useful to distinguish between two basically opposed ethical approaches to reality and human technological interventions. The approaches are presented in an ideal-typical way. In real life choices will often embody a kind of mixture of the two approaches. Yet it remains of crucial importance where one chooses one's starting point.

The two approaches can be rendered as 'essence precedes existence' versus 'existence precedes essence'. The first approach, essence precedes existence, holds that reality has meaning and value that underlie human existence. Because of the frailty and mortality of human existence and the existence of evil this meaning often is elusive and needs to be discovered and elaborated by human beings and given shape in everyday life. But reality has a value in itself independent of its usefulness for mankind. So, fundamentally, 'meaning' is not a construct of the human being and the experience that life makes sense is not an emotional illusion but refers to the ultimate reality about mankind. In contrast, much contemporary ethical analysis assumes that existence is the raw material of ethics. This approach holds that the task of humanity is to construct meaning and values which will guide our choices against the backdrop of circumstance – in other words, it holds that existence precedes essence.[125]

We take the first approach, essence precedes existence, as our starting point for ethical analysis. We call this 'meaning-based ethics' since it starts from the presumption that life and reality harbour meaning and that meaning ultimately is not something we construct or produce. To discover and experience this given meaning it is necessary to observe fundamental ethical principles and values. In other words, fundamental ethical principles and values are to be observed to come to an understanding and experiencing of given meaning. We want here, however, to add one observation. We favour a modest version of meaning-based ethics. Meaning-based ethics does not assert that we have perfect detailed knowledge of what is proper and improper. On the contrary, ethical judgement must be based on painstaking analysis undertaken in the light of the most complete scientific knowledge available. But this process of learning how to apply values to any particular situation is a journey of discovery, not of quasi-artistic creativity and aesthetic judgement. Our choice for meaning-based ethics is founded on our belief in the priority of universal

124 It is also against this background that the European Union has established a Charter of fundamental rights of the European Union, Nice 7 December 2000.

125 For this rendering of these two positions we gratefully used the formulation Dr. Asher Meir made on behalf of the website www.meaningbasedethics.com

ethical principles, and on our belief that human faith traditions, when combined with introspection and reason, are an indispensable source of guidance regarding the specific content of these principles.

We see that according to meaning-based ethics, prevailing conditions, whether social, scientific or economic, can never dictate what is right and wrong. In fact, so-called 'ethical' choices founded solely on circumstance without taking into account the prior meaning structure of reality will harm both reality and ourselves. We could liken this course to a physician who pays sole attention to the patient's symptoms, his subjective experience, and neglects the underlying illness. In the end, both the symptoms and the illness are likely to progress. The wise physician acknowledges the critical role of noting symptoms to make a diagnosis and of treating them to palliate the patient, but views his primary role as conquering disease.

One area of those fundamental ethical values concerns the human being itself. The question whether human life a priori is meaningful is closely related to the question of the value of human life. Because we believe human life to have inherent meaning, we also belief it has an unalienable value. The human being has a dignity that claims unconditional respect and that determines what kind of actions are morally right. This means that a philosophically founded anthropology is important as a fundament for the ethical discussion. The fundamental question of anthropology is what is the true nature of mankind and not just what human beings can do or how they behave. Experimental sciences can give an answer to the latter questions and ethics should take into account the answers, but only anthropology can account for the transcendental dimension of the human being. Without this anthropologic fundament, ethics would lose its normative character to become a simple exposition of the different situations in which man can be and the different options he can chose according to his personal vision of life or the values that are generally accepted in society.

1.3. The role of ethics in biotechnology

New advances in biotechnology offer us unexpected possibilities of relieving human suffering and treating human diseases previously thought incurable. At the same time many of these powers give us possibilities of intervention on human life that profoundly touch our concerns regarding human dignity, raising new ethical questions. These controversies will always accompany biotechnology because it involves the manipulation of the building blocks of life itself. This surely does not imply that biotechnological discoveries always undermine human life, often quite the contrary.

The ethical reflection about the morality of the different procedures is an intrinsic exigency of biotechnology itself since it can affect the human being, which is its agent, its subject and its finality, for good but also for evil. It appeals to him as an intelligent and free agent that must realise itself through free acts by choosing what is good. Scientific activity is a kind of human activity and consequently must be evaluated in the light of the moral principles that should guide all human action. We cannot separate the world of facts from the world of values. When we look at the scientific practice, science disappears

and we find the scientist, a human being that has to take decisions that are necessarily good or wrong, sometimes ambivalent, but never indifferent. We have to inquire into the human and moral meaning of developments in biomedical science and technology. Biomedical research must be directed by fundamental ethical principles and values, among others relating to human dignity. The ethically correct research and application of scientific advances is a task (competency) of the human free decisions.

It is clear for everybody that we are not obligated to do the impossible: ad impossibilia nemo tenetur, but the opposite is not always so evident. Many think that when goods as progress, science, and cure of diseases come into play, researchers have the moral obligation to explore all the possibilities: the promises of biotechnology seems to require that no limits are set for the investigations. This is again the old problem of the means and end. Can the goodness and justice of some ends justify each means to obtain them?

The morality of an action cannot only be deduced from its therapeutic benefits. The different possibilities that science offers us are only technical possibilities. The limits of the technical advances do not have to determine the limits of the morally acceptable. We can use advances in biotechnology in a manner according to fundamental moral principles or use them against the respect due ourselves and every human being.

Ethics does not imply a limitation of the methodological and thematic autonomy of science and biotechnology. Neither should it be an obstacle to the advance of biotechnology. It is meant to give biotechnology and biomedicine its true dignity as an instrument for the well being of the human person. The fundamental ethical question for biotechnology is whether the human being has inherent dignity that claims unconditional respect and involves limits to the technical power of some over others or whether the human being in its bodily existence can be reduced to raw material for the manipulative power of technique.

1.4. Ethical perspectives

How can we determine whether or not an action is morally acceptable? How should the notion of human dignity function in ethical questions related to biomedical research? Ethics has formulated (at least) three (families of) theories that help to answer those questions. These theories are related to the elements that can be distinguished in a human action, viz. the action, including any technique that may be used, the acting person, and the goal or consequences. Each of these elements corresponds with a specific ethical perspective on the human action and an ethical theory to answer the question of its ethical acceptability.

We discuss three perspectives on the (morally) good life.[126]

126 Here only a simple sketch will be given to provide a basis for the following discussion. Every handbook on (medical) ethics will contain a more extensive presentation of these theories.

1) Action itself

Although all aspects of an activity or action are relevant for understanding its full ethical significance we have to distinguish what the action is from why it is done and what are the consequences. The act itself must be according to the relevant moral principles and the rules derived from them, independent of the intentions of the agent and his objectives. For instance, research with human subjects requires adequate informed consent and should fulfil the principle of proportionality of the burden on the experimental subjects and the benefit of the (expected) results. These requirements cannot be put aside regardless of the expected benefits of the research. When the action itself is wrong, neither good intentions nor the benefits obtained could make it good. It is often not as clear as this, as in the example of whether an action is morally objectionable in itself. To evaluate this one requires knowledge of the relevant moral principles as well as of the specific techniques involved.

The moral theory asserting that an action should observe the valid principles and norms to be an ethically good action is deontology (from Greek: deon = duty) Well-know principles in bioethics are respect for life, care, beneficence, non-maleficence, autonomy (from which the requirement of informed consent is derived) justice, confidentiality.

2) Consequences of the action

Consideration of the consequences of an action in a particular situation is also important for its moral assessment. This is especially true in medicine where improvement in the condition of patients is sought. Thus, an ethically good treatment is firstly a medically good treatment that benefits the patient. Moral theories that evaluate the ethical quality of an action by its ends or results are teleology, consequentialism and utilitarianism.

But even though the ability to treat or heal suffering persons is a great good, not all methods of achieving a desired good are morally or legally justifiable. Often an action aiming for a good end involves a negative side effect. Here the moral question arises: what proportion of (expected) benefits to risks and burdens to the patient should there minimally be for a treatment to be offered? This concerns the principle of proportionality which is very central to medicine. Informed (or proxy) consent of the patient is a necessary requirement for a treatment, but not a sufficient justification. Desperately ill patients could be tempted to accept any 'treatment', but should be protected against themselves and against exploitation by eager, good-intentioned medical researchers. We are not always obligated and sometimes not even allowed to do what is technically possible when other interests, such as the dignity of the person or the moral quality of society, would be harmed.

Important in the application of the proportionality principle is that the foreseen but unintended burdens and risks result from the same action as the intended benefits. An intrinsically ethically objectionable action cannot be justified, even when the outcome of that wrong action may be beneficial. One could treat several patients by killing one and transplanting his organs to the others. This, of course, would be unacceptable. Here the action of killing is not accidental to the transplantation. The intention is not only to cure some persons, but also to

cure them by killing another. But neither the means we employ to obtain an end nor the end can be considered in isolation from the moral good of society and each concrete individual. Foreseen unintended negative effects are morally justifiable only when the good and the evil effects proceed equally directly from the action. In other words, when the negative effects are unavoidable in realising the positive effects and their balance is proportional.[127]

A principle similar yet distinct from proportionality is subsidiarity. Here, in a situation where a certain end can be pursued pretty much equally well along different ways, the way that is easiest, cheapest, least invasive and burdensome and/or ethically least problematic should be followed. This can be seen as a form of good stewardship.

Precautionary principle

A final but important observation. The theories discussed here concentrate on the effects of an action or an enterprise. So far we have considered mainly the immediate consequences, e.g., of medical treatment. But this is not enough. It is also important to take into account the long-term consequences of certain choices, consequences not only for those individuals directly involved but also for society at large and therefore for many people and maybe even for future generations. This is especially true for biotechnological interventions since they may not only have long-lasting and irreversible effects for individuals but also for society at large. In this context we want to appeal to the precautionary principle that is internationally accepted in the context of environmental risks of human activity including biotechnological applications.[128] The precautionary principle is primarily a policy rule based on the principle of responsibility for future conditions for mankind and for future generations[129] and related to the virtue of prudence. A well known way of rendering it is: "If there is a reason to believe that a technology or activity may result in harm, and there is scientific uncertainty regarding the nature and extent of that harm, then measures to anticipate and prevent harm are necessary and justifiable."[130] In our opinion this principle should not only be applied to situations of risks for environmental harm, but also when there are risks for social and ethical 'harm'. With the latter we refer to a situation in which certain practices can be expected to undermine fundamental principles and values of our culture and our societies.[131] We stress the importance of this since the short-term effects of new technologies seem to be obvious and positive whereas the negative effects will be visible only in the long run and often remain more diffuse but

127 For a more extensive introductory discussion of the distinction between foreseen and intended and between permitting an undesired course of events and bringing it about and about the principle of double effect, see, Reich WT. Encyclopedia of Bioethics. New York/ London: The Free Press, 1978: 33-8, 424-5.

128 Commission of the European Communities. Communication from the Commission on the Precautionary Principle. Brussels: Commission of the European Communities, 2000: 13

129 Jonas H. Das Prinzip Verantwortung. Versuch einer Ethik für die technologische Zivilisation. Suhrkamp Verlag (1979).

130 Raffensperger C, Barrett K. In defence of the Precautionary Principle. In: Bailey B, Lapp□ M (ed). Engineering the Farm. Ethical and Social Aspects of Agricultural Biotechnology. Washington, 2002: 162

131 It seems to be in this sense that the European Group on ethics in science and technologies to the EC in its opinion on ethical aspects of human cell research and use (Opinion no 15, 14 November 2000) refers to the precautionary approach (in section 2.7, p. 16) although the precautionary principle is not invoked as such.

nevertheless have a profound impact. (e.g., modern traffic that enabled an enormously dynamic economic and social development, but also results in many traffic accidents and victims, pollution, wasting of resources; the victims virtually remain anonymous to the larger public and the latter two effects are long-term and diffuse effects).

3) The agent

Conformity of an action with the norms is insufficient for a moral evaluation. The morality of a human action is also determined by the intention of the acting person. The intention is the motive of the agent to perform or regulate the action, in which 'motive' involves a cognitive as well as an emotional and volitional element. People evaluate a wrong action that happened by mistake (unintentionally) differently from when it is done on purpose (intentionally). An operation on a patient with the intention of curing him, but that by accident results in his death is not the same as giving a patient a drug to kill him. And the physician who not only foresees that a medically required cancer treatment will cause a lot of suffering to the patient, but who would intend that suffering would not be looked upon as a very ethical person. So intention, the attitude of the agent, is important for the ethical evaluation of an action. For a human action to be ethically correct, the intention, the moral attitude and disposition of the agent should be ethically correct. A person who knows the good to be done, but who lacks the will or moral strength to do it, is not a morally good person.

This brings us to the concept of virtues. Virtues can be seen as internalisations of principles and as the embodiment of values in the life and conduct of a person. A virtue is a quality of the morally good person. Virtues help a person to behave in a certain desired way, enable the person to achieve certain (moral) goods.[132] Well-known virtues in health care are compassion, kindness, prudence, carefulness, attentiveness, courage, fairness, patience. Important virtues in scientific research are creativity, honesty, integrity, courage, openness to criticism. Virtue ethics is the moral theory that describes the ethically good conduct in terms of virtues. It does not concentrate so much on individual actions as on a way of life. The advantage is that the moral life can never be described completely in terms of principles and rules for actions. Everybody performs scores of actions every day and life would be impossible if for all those actions we would have to apply directives. Virtues enable the person to choose the correct way of acting without having to think all the time of concrete directives. Virtue ethics also stresses the importance of personal engagement and dependency in relationships and rejects a concept of ethics as a decision-making theory on the basis of abstract principles. The ethics of care, which has become quite influential especially in the care sector (as distinct from curative medicine), can be seen as a form of virtue ethics.

An important virtue of practical reason is prudence, an intellectual habit that enables a person to see in any given situation what is the good to do and what

132 Cf. MacIntyre A. After Virtue. A study in moral theory. London: Duckworth 19852:191

is not, and how to achieve the first and avoid the latter. This is an arduous task, since there are many factors and circumstances, including the intention of the acting person that can hinder rational deliberation. So in order to apply the moral rules and principles in the right way and with facility, reason must be informed by the virtue of prudence.

Responsibility

In our view each one of these (families of) theories has validity but is at the same time limited. Each concentrates on one element of human action, but an adequate ethical evaluation of human action needs to take all three elements into consideration. In ethical discussions it sometimes seems that these different approaches clash, especially deontology and consequentialism. But since each of the three kinds of theories looks at human action from a certain perspective they are not necessarily in conflict. In certain situations one approach will be most prominent and in other situations another. For example, in curative medical treatment the effects will often determine whether a treatment is medically and ethically acceptable, within the boundaries of certain deontological principles. In contrast, in many situations of caring for people the morality of the behaviour of caregivers will be evaluated primarily in terms of virtues.

We propose an integration of the three perspectives and theories in the concept of responsibility. In human action there is the agent who is responsible and should be ready to give account of his conduct (virtue ethics). The agent is responsible for a certain state of affairs (teleology; e.g., a nurse who is 'responsible' for certain patients). And the action should respond to the principles and norms (incl. laws) that apply in that particular situation (deontology).

It can roughly be said that there are deontological principles that apply always (e.g., no intentional killing, no sexual abuse) or at least prima facie (informed consent, confidentiality; there can be reasons not to observe these). Within the boundaries of these principles the effects determine the morality of actions. Virtuous behaviour and attitude remain important throughout.

1.5. Ethics of stem cell research

In our ethical discussion of stem cell research we will first consider stem cell research itself and then the possible ethical consequences of doing or not doing such research.

The first ethical question with respect to stem cell research is the question of the moral status of the different types of stem cells and of the sources from which they are obtained. A central issue in this respect is the moral status of the human embryo, as a potential source for embryonic stem cells. In dealing with this question we first give a biological description of the beginning of human life and subsequently present a philosophical analysis. Granting at least a certain degree of protection we are confronted with a classic moral dilemma: is it ever right to cause some evil to achieve a greater good? In the case of stem cell research the question is whether it is morally licit to produce and/or

use living human embryos for the preparation of ES cells. In case this is morally rejected the ethical problem can be raised whether the use of embryonic stem cell lines or of the differentiated cells obtained from them should be seen as ethically problematic for being a kind of complicity with the destruction of embryos.

The commercialisation of stem cell research raises a number of concerns about possible commodification of the human body and about the value of the human body and each human individual.

After considering the ethics of stem cell research itself we will assess the consequences of approving or prohibiting such research for human dignity and society. What will be the effect of sacrificing embryos and the commercialisation of cells derived from them on respect for life in medicine and in society at large? Would prohibition of embryonic stem cell research dangerously restrict scientific inquiry and signify callousness toward those who suffer serious illnesses? Who will be able to use these new therapies if they are developed? These are some of the many ethical questions we will grapple with and try to answer.

2 THE STATUS OF THE HUMAN EMBRYO

The issue

One of the most crucial ethical issues in the debate on human stem cell research concerns the moral status of the human embryo and of stem cells themselves. Fresh embryonic stem cells can only be harvested from human embryos that are destroyed in the process. How the embryo is defined and evaluated in its different developmental stages is the basic premise for questioning whether medical procedures involving death of the embryo are morally permissible. A more general rendering of the issue is to question whether the value of a human being rests on certain qualities or on the fact that it is a human being. In other words, has human life an inherent value simply because it is human?

If, from the beginning of its existence as a distinct being, i.e., fertilization, the human embryo is to be considered as a human being with the moral status of any human being, research on embryos should be conducted within the same guidelines as those on children that cannot give consent themselves. The internationally accepted position is that research involving these subjects is only ethically correct when the person may personally benefit from it and is put at no significant risk of harm. Clearly, killing embryos to extract their stem cells would be unethical within this perspective. If, by contrast, an embryo is just a clump of human cells which might become a (fully) human being after some time, it will be viewed as scarce and therefore valuable human tissue that can be used and destroyed for good medical research without any serious ethical qualms. Embryonic stem cell research will be considered morally acceptable and there will be even a moral imperative to explore the medical potentialities of such research particularly because of its therapeutic and scientific benefits. In addition to these two positions there is a variety of intermediate positions with respect to the status of the human embryo. These positions hold that the early human embryo is not to be viewed as a human

being in the sense of a human person and therefore does not merit the same degree of protection. As a potential human being it has a certain status that is considered to increase as the embryo develops. Hence, there can be good reasons to use early embryos for research.[133]

Though these latter two positions may differ with respect to the restrictions they would put on embryo research,[134] at a fundamental philosophical level all defenders of embryonic stem cell research separate the biological beginning of the human being from the beginning of the human being in a moral sense. They hold that while the embryo represents (developing) human life, no personhood can be attributed to it and it does not have the moral status of a human being.

Current biotechnological advances closely related to embryonic stem cell research, such as cloning, creation of hybrids and parthenogenesis, raise yet more questions requiring an urgent answer about the nature of the early embryo.

Related to the question of the status of the embryo is that of the moral status of stem cells. Should they be characterised as specialised somatic tissue or as equivalent to an embryo? This question hinges on an understanding of the stem cells' potentiality and is closely related to the potentiality of clones and parthenotes to become human beings.

Discussion on the moral status of the human embryo will consist of three steps. First, we will look briefly at some of the main documents from discussions in the EP over the last two decades on research with human embryos.

In the second step we will look at the human embryo from a biological perspective and deal with some problems at this level. Although biology in itself can never answer the question of whether or not an embryo should be seen as a person, obviously philosophical and anthropological reflection should comprise biological knowledge and insights in formulating a view of the embryo that biological research should take into account.[135] In the third step a philosophical perspective will be given, including discussion of some problems in this respect.

2.2. The European discussion on embryo research

There are two major European institutions that have generated a context of regulations and agreements also in matters of bioethics. These are the Council of Europe and the European Union In this paragraph we will present and discuss the major documents that have been produced by one of these two organisations and have in the past influenced the member states to some

133 For a short presentation of this discussion see: A Kahn. 'Therapeutic' cloning and the status of the embryo. In: Council of Europe Publishing (Ed.) Ethical eye: Cloning. Strasbourg: Council of Europe 2002:103-15

134 The different legal regulations with respect to embryo research in various countries reflects a variety of ethical and juridical positions on this point; for an extensive review see: Gratton B. Survey on the national regulations in the Europe regarding research on human embryos. Brussels, June 2002; http://europa.eu.int/comm/european_group_ethics/ docs/nat_reg.pdf>

135 D'Agostino, F. Bio□tica. Turin, Giappichelli, 1999: 3 ed.

extent, and perhaps continue to do so. The diversity among the member states will become clear by the differing opinions and regulations.

The Council of Europe is an intergovernmental organisation. It aims to protect human rights, pluralist democracy and the rule of law. The European Union is based on the rule of law and democracy. Its member states delegate sovereignty on questions of joint interest to institutions of the Union as a whole.

2.2.1. The Council of Europe and embryo research

The Parliamentary Assembly has over the years adopted a number of Recommendations on bioethical issues. These Recommendations are not binding for the member states but are not apolitical and have certain influence on policy and public opinion. Both Recommendation 1046 (1986) and 1100 (1989) deal with the use of human embryos. They both point out the biological and genetic continuity of the human embryo after fertilisation throughout its whole developmental process. The Recommendations require embryos to be treated with respect due to human dignity. In R 1046 the Parliamentary Assembly more specifically calls on governments of the member states to forbid the creation of human embryos by IVF for research, research on viable human embryos and experimentation on living human embryos, creation of identical human embryos by cloning or any other method and fusion of human embryos. At the same time the Assembly recognise that a variety of opinions exists on the use of the embryo or foetal tissue and ask for an initiative that should lead to a common legal instrument in the issues at stake.

The most important document from the Council of Europe on matters of bioethics is the "Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine". Some of the member states have ratified this convention, others not (yet). The United Kingdom, for example, has not signed it, probably because the UK has a more permissive regulation of embryo research than the Convention allows. Article 18 of the Convention deals with embryo research. It states in 18.1 that "where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo". There is ambiguity in "adequate protection". What does this entail? Those who want to protect the embryo against destruction read in this article that research is only allowed if it is in the interest of the embryo itself (like the Recommendations mentioned earlier). But those who want to use the embryo in research that leads to the death of the embryo take this provision to mean that destructive use of embryos in research is only allowed for good medical scientific reasons, not just for any research. So, article 18 deals with an important issue in an ambiguous way. The explanatory report that contains extensive clarifications to other articles does not clarify this article. Apparently, the plurality of opinions did not allow any further stipulation.

Article 18.2 states that "the creation of human embryos for research purposes is prohibited". This article is clear in itself and valuable for those who want to grant full protection to the human embryo. But here the legal weakness of the

Convention becomes apparent. The states that do not want to fulfil this provision do not ratify the Convention or make a reservation in respect of this (or any other) provision of the Convention. The Convention provides for the possibility of making such a reservation

Despite ambiguities such as those mentioned, the Convention clearly exerts a moderating influence on the acceptance of biomedical research or interventions that imply deliberate destruction of human embryos.

On October 2, 2003 the Parliamentary assembly of the CoE adopted a resolution on Human stem cells in which on the basis of earlier resolutions and recommendations a prohibition is favoured of research in which embryos are deliberately destroyed.[136]

Embryo research in the European Union

The status of the human embryo and the related permissibility of therapeutic or destructive embryo research has been one of the most debated topics in the European scene. In 1989 the European Parliament adopted a resolution on artificial insemination in vivo and in vitro. This resolution does not allow the use of embryos to cultivate embryonic stem cells, let alone to create (clone) embryos for research. It states, among other things, that experiments on human embryos in vitro should be forbidden.

Issues related to developments in human genetics were intensively debated in 2000/2001 in a series of hearings organised by a broad "Temporary committee on human genetics and other new technologies in modern medicine". This committee drafted a concept resolution.[137] Though the resolution was rejected after a long and confusing debate, it contains several statements that were broadly supported in the European Parliament. With respect to embryo research it is more permissive than former resolutions that essentially only approved therapeutic embryo research. The proposed resolution accepts the use of surplus embryos e.g., for the cultivation of human embryonic stem cells. The main reason rejecting the resolution was probably that no consensus could be reached on the issue of human therapeutic cloning. The resolution recommended a ban on all human cloning, while some parties wanted to leave open the possibility that 'therapeutic cloning' would be allowed under strict conditions.

In 1998 the European Parliament accepted a resolution on cloning.[138] In it the EP invites the member states to ratify the Convention of the Council of Europe on the protection of human rights and human dignity and its additional protocol that forbids human cloning. Still, the issue of therapeutic cloning was not made completely clear. More recently the European Parliament's Committee for the Environment and Public Health has backed calls from fellow members of

136 Human stem cell research. Resolution 1352 (2003) adopted on October 2, 2003. (Doc. 9902)

137 Temporary committee on human genetics and other technologies in modern medicine. Unofficial version of the Fiori resolution (A5-0391/01) as amended before the rejection in the final vote on 29 November 2001 (December 12, 2001).website: <www.europarl.eu.int/committees/genetics_home.htm>

138 Resolution on the cloning of human beings. Doc. B4-0050/98. PB C 034, of 02-02-1998, p. 0164; also Human cloning. Texts adopted by the European Parliament on 07-09-2000 (B5-0710, 0751, 0753, 0764/2000).

parliament for a comprehensive ban on human cloning. This demonstrates the sharp division among the members of parliament, reflecting the dissension in society with respect to embryonic stem cell research using 'surplus' embryos or embryos created explicitly for research purposes. The division is underlined by the fact that in 2000-2001 the European Parliament, the Council of Europe and the Commission of the European Union endorsed the Charter of fundamental rights of the European Union.[139] In article 3.2 this charter pleads for a prohibition of 'reproductive cloning' of human beings. Since in a draft it asked for the prohibition of the cloning of human beings, it should be understood that there was no consensus to also ask for a prohibition on research cloning.

Meanwhile, the European Group on ethics in science and new technologies presented its opinion on the ethical aspects of human stem cell research. In this informative document the European Group takes a relatively cautious position. It defends the use of 'surplus' embryos for the cultivation of embryonic stem cells. However, it considers the creation of embryos for embryonic stem cell research ethically unacceptable when spare embryos represent an alternative source.

Thus, the European scene on human embryonic stem cell research continues to demonstrate dissension and confusion. Leading bodies are for the moment taking a relatively cautious position, not rejecting all forms of cloning, but not funding research in this field either. At the same time scientists and industries are trying to keep open all research possibilities.

2.3. Biological perspective

The beginning of a human embryo

To be a human being means to be a specimen of the human species. So from a biological point of view the question whether a human embryo is a human being is whether a human embryo is a member, a specimen of the human species.

As a rule a human being begins as the result of the fusion of an egg cell with a sperm cell, resulting in the zygote, essentially a single cell with the potential of producing every cell in the adult body. Sometimes a zygote can result in two babies, monozygotic twins, of which one did not originate at the gamete fusion. Furthermore, the early embryo can be split into two embryos in vitro. If cloning by somatic cell nuclear transfer or by parthenogenesis would become possible, these would constitute ways other than fertilisation in which a zygote could originate (see further § 4). This means that although a fertilised egg is normally the beginning of a human being, fertilisation is apparently not an essential requirement for a human being to come into existence. The central question here that science must resolve is to determine what kind of entity the zygote/early embryo actually is, independent of the way it came into being, and whether this biological entity has to be seen as a specimen of the human species. To answer this question one must consider the embryo in the whole of

139 Charter of fundamental rights of the European Union, (2000/C 364/01) signed on December 7, 2000 in Nice by the Member states of the EU.

its life from its beginning to its end. Without this broad view it is impossible to correctly analyse the status of the embryo at each stage of its development. A simple morphological analysis appears to be insufficient to determine whether cells with an embryonic phenotype are just multiplying human cells or a human zygote.[140] This distinction is essential since a group of cells that has a human genome and is able to multiply but does not form an organic unity cannot be considered a human being. Hence, a necessary condition for a human biological entity to be considered a specimen of the human species is that it forms an organic unity that under the required environmental conditions can go through a full ontogenesis of the human species. But is this also a sufficient condition?

2.3.2. Human embryo and human being

A major area of debate is the significance of the potential of the embryo to develop as a specimen of the human species. This potential is not always realised. Many embryos die before or shortly after implantation or even later in pregnancy. Therefore, in the natural course of events, not every embryo has the actual potential to develop as a human being. At issue here is the determination of the configuration and essential characteristics of the biological entity that should be seen as a human being. Morphological characteristics and the presence of human chromosomes in the cells are not sufficient criteria to determine whether we are dealing with a human being. Human life cannot be reduced to genetics. Genes are necessary, but not sufficient, to explain the embryological development and existence of a human being in all its aspects. There is a second level of information, not contained in DNA, though the DNA is required, but in the specific structure and content of the cell that is able to start the developmental process of a specimen of the human species. The fusion of (normal) male and female gametes switches on this process. When this process begins there is a new specimen of the human species.

It is clear that a single-celled embryo will become a full-grown, complete organism through a series of successive, interconnected steps. This process is guided by the information contained in the genome, which is activated by signals coming from interactions within the embryo itself and with its environment. Individual events of this process, such as cellular reproduction, differentiation of tissues and formation of organs, are realised successively, but the growth and development of the organism as an individual entity are continuous. There is no point at which the embryo is not an active protagonist of its own development and at which this embryo does not have the potential to become a newborn human baby. The gradual acquirement of the final form implies that the embryo is always the same individual who is acquiring the shape and form typical for each stage of development. Current experiments in which the first two cells of a mouse embryo were tracked showed that they have different fates. One cell tends to produce those that make up the embryo body. The other gives rise to the placenta and other supporting tissues.[141] Scientists think that the point at which the sperm enters the egg may set up

140 E.g. think of embroid bodies in teratocarcinoma that morphologically look like embryos but are not.

141 Pitrowska K, Wianny F, Pedersen RA, Zernicka-Goetz M. Blastomeres arising from the first cleavage division have distinguishable fates in normal mouse development. Development 2001; 128: 3739-48.

the early axes of the embryo, possibly by altering the cell's internal skeleton.[142] These results are the first confirmation that the early embryo is not a uniform mass of cells. The laying down of the mammalian body plan begins from the moment of conception. Immediately after fusion of human gametes a new human cell equipped with a new information structure begins operating as an individual with a very definite orientation and symmetry. The coordinate structure of this new unit is the new genome with which the one-cell embryo is equipped. This genome identifies that organism as biologically human and specifies its individuality.

We take a lengthy quote from a statement of eleven Italian professors in (bio)medicine that explains very clearly the biological status of the human embryo.[143]

"The newly conceived presents itself as a biologically defined reality: it is an individual that is completely human in development that autonomously, moment by moment without any discontinuity, actualises its proper form in order to realise through intrinsic activity, a design present in its own genome.

The formation of the newly conceived, from fertilization until birth, and in the whole process of growth and development afterwards, reveals a projected end. Its vital cycle and its development are characterised by three biological properties that are well known: coordination, continuity and graduality.

Coordination is a process where there exists a sequential and coordinated interaction of molecular and cellular activities under the control of the new genome that is modulated by an uninterrupted flow of signals, transmitted from cell to cell and from within as well as outside the cellular environment. This property implies, or more properly, demands, a rigorous unity of the being that is in constant development in space and in time.

Continuity allows the new vital cycle to proceed with successive events one after the other "without interruption".

Graduality is a property that "implies and demands a regulation that must be intrinsic to every single embryo" and allows it to reach, gradually, its final form.

In this developmental process it is impossible to identify a line of demarcation at which an embryo turns from a 'non-human' into a 'human' being. The early embryo is a specimen of the human being and, as such, a human being.

In answer to the objection that, at five days or fifteen days, the embryo does not look like a human being, it can be pointed out that this is precisely what a human being looks like -and each of us looked like- at five or fifteen days of development. Our inability to visually recognise the humanity of the embryo does not mean that it is not human.

142 Pitrowska K, Zernicka-Goetz M. Role for sperm of the early mouse embryo. Nature, 2001; 409: 517-521.

143 Declaration of 11 professors from five Faculties of Medicine and Surgery of the Universities of Rome, Organisers of the Conference on The Embryo as a Patient held at the La Sapienza University of Rome, 2002

Human embryo and human individual

An argument that is often put forward to negate the existence of a human individual from the moment of conception is the possibility that an early embryo can split into a pair of identical twins. Because of this possibility –so the argument runs- we can speak only of a definitive human being at the moment the cells of the blastocyst have lost their pluripotentiality and are not able to give rise to a new individual when separated from the original group of cells. This is at least the case at day 14 after conception when the 'primitive streak' is formed. There is at present no theory that is able to explain why, or when, a zygote can divide into two and naturally produce two or more identical twins. It is possible that the forming of twins is pre-programmed from the moment of fertilisation itself. The possibility of twinning may be an indication that the fusion of the sexual gametes is not the only way to give rise to the conception of a new human life. (In § 2.4.3 we come back to this problem).

From these biological data we conclude that a human embryo, including a fertilised egg cell, is a human being with its own identity that is the protagonist of its biological existence.

2.4. Philosophical considerations

2.4.1 The moral status of the embryo

A philosophical consideration is needed to interpret the data available from biology with respect to their ontological and anthropological significance.

The biological data clearly show that the human embryo is a specimen, a member of the human species. But science itself cannot tell us how we should evaluate that. That depends on a broader view of the human being and human existence. On the moral status of the human embryo there is a wealth of literature and in the context of this report we do not pretend to give an overview or summary of the various positions and arguments. We will briefly present our view and the main arguments for it.[144]

The human being manifests itself in the first place in its bodily existence. When we meet somebody we first see the body which can be described as a biological organism. But it is common human experience that the human being is more than the ordered conglomerate of cells of which it consists from a biological point of view. The human being can normally perform activities that are typically mental or spiritual, such as knowing, imagination, evaluation, creativity, religiosity. In this sense the human being attains a meaning that transcends the mere biological meaning. But those activities have the body as its substrate, they are informed by information that is acquired by the senses and they influence behaviour and interventions in external reality by the body.

144 Three recent publications that argue for a position similar to that defended here are: Forsythe CD. Human cloning and the constitution. Valparaiso University Law Review 1998;32 (2):469-542; Evans RW. The moral status of embryos. In: Kilner JF, Cunningham PC, Hagar WD (ed.) The reproduction revolution. Cambridge, UK: Eerdmans 2000:60-76; Schockenhoff E. Der vergessene K□rper. Über die Einheit von Person und menschliche Natur. Zeitschrift für medizinische Ethik 2002;48(3):271-281.

Thus, the body is integral to having a self and constitutive for the human being. At the same time, because of those activities, we recognise that the person is more than his body as a material and biological entity and also has an existential meaning and a transcendental value that includes the body.

These experiences demonstrate that we can best conceptualise the human being as a single being with a duality of dimensions, a material and a spiritual dimension. (We use the word spiritual in a broad sense, encompassing the mind and mental phenomena). We speak of dimensions in order to avoid the word 'parts', which would imply a form of dualism. On the other hand we consider both the material and the spiritual dimension as irreducible realities. We reject a philosophical substantial dualism because, among other reasons, it raises the insoluble problem when the spiritual dimension is united with the biological.[145] Nor do we agree with a form of monism in which the spiritual dimension, in particular consciousness, would emerge from the material dimension, i.e., the functioning of the brain, and not represent a qualitatively different dimension of reality. This latter position, though popular in neurosciences, does not take seriously the religious and spiritual experiences of humans through the ages who have testified to the reality of a spiritual world.

This leads to the conclusion that from the beginning of its bodily existence the human being has a spiritual dimension and should be seen as a human being in the full sense, a human person. We do not pretend to be able to fully understand the relationship between the biological and the spiritual. The origin of each human being transcends its beginning and bears the mark of a secret that resists a full scientific and even philosophical explanation. The ethical implication of this position is that the human embryo, from its beginning, deserves the full protection of every human being. We do not defend an absolute protection since that is not provided to anybody and in real life is impossible.

A potential human being?

An argument against our position asserts that a fertilised ovum is not a human being but is rather a potential human being and consequently does not deserve full protection. This position does not take into account a distinction that in our opinion is vital in this context. This is the distinction between active or natural potentiality ('can develop as') and passive potentiality ('could become'). The ovum and the sperm that exist independently of each other, have the passive potentiality to become a human being. The potentiality of sperm and ovum for actualising a new human person depends on the presence of an ovum or sperm cell, respectively. The gametes are human life, but not the life of a human being. The gametes have to undergo a biologically fundamental transformation into another kind of biological entity to become a human being. In contrast, the zygote formed by the union of ovum and sperm has the active potentiality for biological development as a human organism towards a full-grown human being (cf. 2.2. and 2.4.1. supra). The zygote need not undergo any biological transformation into another kind of organism to be able to go through the

145 This does not mean that we deny that from a theological perspective it can be meaningful to speak of ensoulment, but such a discourse is not generally accepted in our society.

normal species-specific biological development of the human species. Therefore, the zygote is not a potential human being in the sense of 'could become', but a living and individualised organism with its own internal program, that has the intrinsic potential to develop in the species-specific way. In realising this intrinsic potentiality the zygote depends on the external environment, but it assimilates the external stimuli according to its own laws of development. The physical relationship with the mother and the presence of the right components of the medium are essential requisites for further development of the embryo into a full-grown human being. But this is an extrinsic dependence and it does not mean that the embryo lacks internal autonomy. That many embryos abort spontaneously can be due to chromosomal abnormalities of the embryo itself or in the components of the medium and again does not contradict the full humanity of the embryo, just as high infant mortality does not reduce the full human status of infants.

Individuality

One argument against the before-mentioned position is that a being whose individuality is still unsettled cannot be considered a human person. But here another distinction should be taken into account, viz. the distinction between metaphysical and numerical unity.[146] Many hold that continuity as a key factor in defining a human being implies a single entity.[147] The human person as an individual, living, biological organism would begin when the cells that will form the foetus (as distinct from those that develop into the placenta) become specialised and begin to grow and function in a coordinated manner. Before this point it would be incorrect to speak of an individual human organism, since each cell or group of cells has the capacity to separate from the rest of the embryo and develop as a new individual organism.

But individuality is compatible with divisibility. The identification of an embryo as a human being is not so much based on the indivisibility of the embryo, but rather on its maintaining its dynamic unity and organic system. The problem of division is a secondary one. At the moment of splitting a new individual grows out of the material of the first without the first losing its ontological status. Although the genetic code is identical, they are distinct ontological individuals since they form two distinct organisms for which all that has been observed for the human embryo is valid. Twinning may be an indication of the capacity of self-regulation and compensatory repair within early life, and not the lack of individuation in the early embryo.

2.4.4. Personhood

A last objection we want to mention briefly is that the human embryo may be a human being but cannot be considered a human person deserving full protection. A human being in the biological sense is only considered to be a full human being in the moral sense on the basis of demonstrating certain characteristics, certain 'indicators of humanity', like having at least the

146 Colombo R. Statuto biologico e statuto ontologico dell□ embrione e del feto umano. Anthropotes, 1996; XI: 132 ss.

147 Olson E. The Human Animal: Personal Identity Without Psychology. New York: Oxford University Press, 1997.

possibility of attaining consciousness or having the capacity to suffer. Only human beings that fulfill certain criteria can be considered human persons.

We refute this position for two reasons. Firstly, it implies that during development the human being attains some essential characteristics that make it into something else, namely a human person. This entails a form of dualism. The status of the human being before that moment becomes unclear and it would be difficult to identify a moment in the continuous development when an embryo's moral status goes from 'less than a human person' to 'fully a human person' (cf. § 2.3.2).

Secondly, we refute this objection for a prudential reason. Our position forms the clearest basis for the full protection of every human being. The only requirement for deserving such protection is belonging to the human species and therefore to the human moral community. No other characteristics are required. Any other position with respect to the human embryo implies that certain functional characteristics form the condition for belonging to the moral community of mankind. Hence, it is in principle possible that other human beings, in addition to the early embryo, do not fulfil that condition. One could think, for example, of comatose or severely demented or mentally handicapped people. This danger is more real to the extent that the required condition is not completely clear and unequivocal. In other words, not granting full protection to the human embryo because it does not exhibit certain characteristics runs the danger that other human beings will also no longer be fully protected.

3 THE MORAL STATUS OF THE HUMAN BODY AND BODY PARTS

3.1. The issue of commodification

The increased possibilities of human body-linked technologies such as stem cell research raise a number of important ethical concerns about the value and status of the human body and its parts, and about proprietary rights and control over human tissues and cells.

Over recent years the human being itself has become the direct target of technology. Medical technologies such as transplantation and regenerative medicine are beginning to utilise human parts in research and treatment of degenerative diseases. As a result, organs, tissues and other body parts have become 'materials' (medical resources) for these procedures and are beginning to be regarded as property particularly in the USA, where this approach seems to be accepted by officials. In contrast, the property concept in Europe is not the basis for dealings with human organs and body parts. The commercialisation of human body parts is one of the critical ethical issues of these new technologies. This issue is most apparent in the competition among biotechnology companies in marketing products derived from adult tissues and cells and from embryos through patents.[148]

This commercial exploitation of human body parts is currently causing three important phenomena: transformation, utilisation and commodification of the human body. Transformation of the human body includes aspects such as

148 Marshall E. The business of stem cells. Science 2000; 287: 1419-21

(xeno)transplantation of organs and tissues and the incorporation of artificial and synthetic structures in the human body. Utilisation of the human body implies the use of the body as a resource of organs, tissues and cells for transplants. These two practices are not, of course, new: extraction of organs from cadavers has been carried out since ancient times.[149]

A more recent and, in our view, urgent problem is the objectification and commodification of the human body and its parts. The increased need for human tissue and cells for treatment and research has raised a commercial interest in human organs and the human body itself is becoming a commodity, an object available for sale. This is not least the case for stem cells. Thus, a fundamental issue is the coherent understanding of the nature of the rights and claims that can be made with respect to the human body and body parts. In this section we try to answer questions related to this issue such as: what are the meaning and value of the human body? In other words, what is the moral status of the human body and its parts? Do people own their own body parts in such a way that they should be allowed to sell them? Who, if anybody at all, has proprietary rights on cells and organs extracted from the body, as a result, for instance, of a medical intervention? Does the use of human body parts for transplantation lead to the commodification of the human person? These issues are discussed from the perspective of a competent adult.

3.2. The status of the human body

The human body in relation to the human being/ person

An important question with respect to the utilisation of human body parts and cells concerns the real meaning of the human body and its parts for the human being. Is the human body an essential constituent of each human being that participates in the dignity of the human person? Or do we have to regard it as something externally added to the human being to be used as an instrument?

We begin our reflection on the meaning of the body for human existence with the common human experience of a dual relationship man has to his body. That is, "I have a body" and "I am my body". The first experience manifests the human capacity to distance himself from his own body and observe it and deal with it to a certain extent as an object. In everyday life people normally look after their body, care for it, dress it, etc. But they can also resist giving in to certain bodily desires, e.g., to eat a candy. At the same time there is no separation between "me and my body". For example, when one takes food one is caring for oneself, not just for the body. Especially in a case of illness the human being experiences more strongly than normal both a certain detachment from the body and the reality of being an embodied being.[150]

This duality in the experience of the relation between the self, the subject on the one hand and the body on the other, reflects a duality in the human being itself. The relation of 'I am my body' stresses the physical, material aspect of the human being. On the other hand, the relation of 'I live my body' shows that

149 Dead bodies were already utilised in ancient Etruria to extract teeth for medical treatment.

150 Toombs S Kay. The meaning of illness. A phenomenological account of the different perspectives of physician and patient. Kluwer Acad Publishers: Philosophy & Medicine 1993; 42: 51-88.

the human being has the capacity to objectify his own bodily existence, can look at himself, as it were, from a distance and can, to a certain extent, deal with his own body as an object and manifest other activities that transcend sheer bodily life. Hence, in our view man is a unique being in which we can distinguish a duality of dimensions, a material and a spiritual dimension as explained in § 2.4.1. Many theories have been offered to explain the interaction and integration of the spiritual and material dimensions in a unique single being such as is each human being. Some believe that body and spirit are distinct substances[151]; others believe that only one of the two realities is a substance, the other being a manifestation of this unique substance[152]; and others deny the substantiality of both body and spirit. Starting with Descartes many theories defend a dualism in the human nature. Man has a body and also a mind (or soul or spirit). The material (res extensa) and spiritual (res cogitans) are mutually irreducible, because the material is spatial whereas the spiritual is non-spatial. Body and soul, since they have nothing in common, cannot interact with each other. In Cartesian philosophy it is impossible for the spirit to causally influence the body or the body to causally influence the spirit, even though Descartes postulated a point of communication between the two in the pineal gland. They are independent of each other, but their activities run parallel, giving the impression of interaction.[153] According to a Cartesian dualism many authors consider the human being as a "ghost in the machine"[154] or a spirit or mind lodged in a material body. The result of this line of thought is that the body is believed to be something added to the human being. In this view the body is considered a purely material entity that does not participate in the moral dignity of the human being. As a consequence, the body is seen as a simple material object that the human being in the sense of the 'I', the subject, possesses.

Against this position we want to argue that the body represents an essential integrated dimension of the human being, that man is a single being with a duality of dimensions. A well-known classical definition of the human person is that of Boethius: "an individual substance of a rational nature".[155] The duality is expressed here in the terms 'individual substance' and in 'rational nature'. The word 'of' expresses the integration. Though here we do not use this classical philosophical discourse, it demonstrates the ancient roots in European culture of the concept of the human being as one being with a duality of dimensions. On the one hand the human being is inextricably tied to the sheer materiality of the body and its parts. Corporality is essential in order to have a human being. But on the other hand the human person can normally perform activities that are typically spiritual (cf. § 2.4.1). So, the body is integral to having a self and constitutive for the human being. At the same time, because of those activities we recognise that the person is more than his body as a material and

151 Psycho-physical parallelism and Dualism

152 Idealistic and Materialistic Monism

153 Descartes R. (1991) [1637] Discourse on the Method, in Descartes: Selected Philosophical Writings. J. Cottingham, R. Stoothoff, & D. Murdoch (trans.), N.Y: Cambridge University Press.

154 Ryle G. The Concept of Mind. Chicago: The University of Chicago Press, 1949.

155 We use the terms human being and human person virtually as synonymous; we do not believe there are human beings that are non-persons But the term human being is used more as a descriptive term and human person as a normative expression.

biological entity and also has an existential meaning and a transcendental value that includes the body.

From this conception of the human body as essentially constitutive for the human being the principles of unity and integrity can be derived. All the organs, tissues and cells form the unique body of this unique human being. The human body is not the sum of its anatomical parts but a whole formed by different parts interacting and depending each on the other. Integrity is a consequence of wholeness. It is the capacity of every human being, indeed of any living system, to remain connected, coherent, whole, and adaptively alive.

Value of the human body

Understanding the human being to be a composite unitary being with a duality of bodily and spiritual dimensions is fundamental to understanding the value of the human body. Since corporality is an essential dimension of the human being, intrinsically tied to human personality and identity, the value we attribute to the human body depends on the value we attribute to the human person.

A basic principle of ethics formulated by Kant and defended by many different philosophical theories and religious traditions is that the human person should not be used merely as a means to an end. He should always be treated as having not only extrinsic but also intrinsic value.[156] Even though some may not consider this principle as an imperative, we can agree that it can at least be seen as an aspiration, an ideal worth striving for. Since the human body is the material manifestation of the person, respect due the human person necessarily involves respect for the human body and its parts.[157] Common experience tells us that our bodies are intrinsically linked to our identity. For instance, if somebody hits us, we ask "why did you hit me?" and not "why did you hit my body?" Something that touches our body is touching us. That is why crimes such as assault and rape are crimes against the person, not just bodily violations. On the basis of the principles of unity and integrity this applies to all parts of the body.

Viewing the human body as a purely material substance that does not participate in the moral dignity of the person, implied in dualistic theories, does not oppose the body's instrumentalisation and (commercial) exploitation. The materialistic concept of the person, which sees the person ultimately as a material being, also tends to see the individual' s body as an object that can be commodified.

An important question in this context is the value and respect due body parts once they have been separated from the individual. Do isolated body parts share in the dignity of the body as a whole that shares in the dignity of the person and if so to what extent? The respect due the different isolated parts depends on the extent to which they contributed to the most essential

156 Kant I. Groundwork of the Metaphysics of Moral. Patton H (trans). New York: Harper Torchbooks, 1785 (1953)

157 Andrews L. My body, my property. Hastings Center report, 1986; 16: 28-38

characteristics of the human being. Not all body parts are considered to have the same relationship to the human being as an integrated whole. A scale can be constructed on which, at one end, are those body parts that are not very intimately associated with the identity of the person, such as hair and nail cuttings. At the other end are the parts considered to be more closely related to the person's existence and identity because they are indispensable for life itself, like the heart, or the gametes because these explicitly carry and can transmit the person's unique genetic information to the next generation.[158] Additionally, specific body parts or structures such as the brain or the genome are closely related to the psychological and the genetic identity, respectively, of the whole human being.[159] Yet, the respect due those parts when separated from the individual living body is not unconditional. They are no longer integrated in the whole and no longer share in the unity of the body as a whole. What we do with these separated parts no longer directly affects the concrete human being from whom they were taken. However, since they were parts of the body of a human being, they continue to have a symbolic value representing that human person. For this reason they should not be treated as simple material things. The question is how they should be viewed and what kind of protection they merit. This will be discussed below.

3.3. Human body parts as property

3.3.1. Property rights as a protection

Our attitude to body parts and substances is closely linked to our attitude to the body. Because of its value and dignity as an essential dimension of the human being that represents the whole person, the body in general is not considered as property in the sense that it has a market value and can be sold or rented without violating human dignity. Respect for the body in a general sense is, for example, demonstrated in regulations with respect to burial or cremation of the dead body. These show that Western societies demonstrate a high degree of respect of the human body, even when dead. It is certainly not considered abandoned material or waste or a commodity, and rightly so. Yet, the question of acknowledging some version of proprietary rights on human tissues and cells is one of the most controversial issues in biomedicine in our time.

Some authors defend the opinion that bodily products separated from the individual body can be considered as a kind of res nullius that belongs to nobody and consequently belongs to the first person into whose hands it falls.[160] But as Matthews comments, the concept of res nullius has only been used in certain specific areas of law and there is no reason to apply it to human body parts. [161]

158 O'Donnell K. Legal conceptions: regulating gametes and gamete donation. Health Care Analysis, 2000; 8: 137-54.

159 The idea of a spectrum of degrees of commodification is related to Radin's idea of indicia of commodification, see Radin M. Contested Commodities. Cambridge, MA: Harvard University Press, 1996:118; see also chapter 4 of this publication, paragraph 5.4.

160 Nuffield Council on Bioethics Working Party. Human Tissue: ethical and Legal Issues. 1995

161 Matthews P. The Man of Property. Medical Law Review, 1995; 3: 251

Others suggest that cells and tissues cannot belong to some individual person because they are res communis (common property). Examples of res communis are the earth and the atmosphere as a whole, public lands, public resources, etc. However, if the body must be considered as the manifestation of the human person, this implies that body parts cannot be considered the property of that person himself, and even less the property of everybody or of the whole of mankind. Sharing a common humanity does not imply a collective right to decide on the substrate of that shared humanity.

In the USA there is a clear tendency to deal with the issue of the use of body parts precisely as (a kind of) private property.[162] In discussing this it is helpful to distinguish between rights relating to the taking of body parts and rights relating to the use and control of body parts. The central rule in the regulations on removal of tissue or body parts is informed consent of the patient/donor or of proxy consent. Without such consent the removal of a biopsy or body parts is considered both ethically and legally a violation of personal integrity and dignity.[163] This applies both to cases in which the body parts are removed during treatment for the benefit of the donor-patient, and to a situation in which organs or tissues are removed in order to be donated to patient-recipients. But when it comes to the regulation of the use of body parts the issue of property rights, and hence of property, is brought in.[164] In Western civilisation ownership in general implies control. To have ownership is to have a cluster of rights or relationships that includes control over: access to the thing (who is allowed to occupy or possess something), use (who is allowed to manipulate and utilise something), and disposition (who may give or sell or will something to another). Most importantly, ownership gives the right to exclude others from access, use and disposition.[165] Thus, an advantage of accepting property rights to one's body (parts) is that they include the power to prevent others from using those body parts in gaining commercial profit.[166] Once body parts are taken from the body and enter the external world, there would seem to be reasons to call on theories of property to provide a legal basis for the protection of the individual's continued interest in his body parts.

These legal and ethical advantages have also led the English Medical Research Council Group on the Collection of Human Tissue and Biological Samples for Use in Research to suggest that tissue samples or collection samples may be treated in law as property.[167] However, there are serious disadvantages to this approach, as will be shown in the next section.

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162 In practice this is clearly evident from the prices that women are paid for their egg cells; in a story from October 2002 regular prices of $ 7,500 are reported for one harvest of egg cells. But for specially 'valuable' persons prices up to $ 50,000 have been are mentioned. See: North Jersey News 7 Oct 2002, http://www.bergen.com/cgi-bin/ page.pl?id =5105001

163 Beauchamp TL, Childress JF. Principles of Biomedical Ethics Oxford: University Press 19944:142-6

164 Nelkin D, Andrews L. Homo economicus: commercialization of body tissue in the age of biotechnology. Hastings Center Report 1998;28(5):30-9; see also chapter 5 of this publication.

165 Grubb A. I, Me, Mine: Bodies, Parts and Property. Medical Law International, 1998; 3: 299

166 Naffine N. The Legal Structure of Self Ownership. Journal of Law and Society, 1998; 25 (2): 193-212.

167 Medical Research Council (1999) Report of the Medical Research Council Working Group to Develop Operational and Ethical Guidelines for Collections of Human Tissue and Biological Samples for Use in Research, Third Working Draft. London: MRC.

Property rights and commodification of human body parts

At issue here is what the ethical meaning and consequences will be of granting property rights to body parts. In the first place, it should be noted that granting property rights on objects involves some type of commodification. The term commodification has two different meanings. It can be used to refer to social practices for treating things as properties that can be bought, sold or rented[168] and to which market theories can be applied.[169] The second main sense of commodification generally refers to an attitude that includes not only actual buying and selling of things but also market rhetoric, the actual thinking of things as if they were sale transactions.[170] The commodification attitude includes three main aspects: a) denial of subjectivity: the commodified thing is something whose experience and feelings need not to be taken into account;[171] b) instrumentality: the commodified thing has only (or mainly) instrumental value;[172] c) and fungibility: the commodified thing is replaceable by money or other objects having an equal market value, with no loss of value.[173]

Objects can be treated as mere commodities when these criteria apply in society, as is the case for many consumer goods or money. However, the use of market rhetoric for things that are not (yet) treated as mere commodities, may further their commodification. Examples of such partial commodities are human labour, sport, copyrights of books and films, etc.

Since human dignity is intrinsically linked to human embodiment an important question related to the issue of property rights on tissues and cells is whether the presented concept of property rights on body parts and its related commercial practices are compatible with such an understanding of the human being.

Commodification of the body

The main concern relating to property rights on human body parts is that these property interests could lead to complete commodification of the human body and that this in turn .01

The view lurking behind considering the human body (parts) as a commodity is a modern form of Cartesian dualism in which the conscious subject is considered the essence of the human being and the body its vehicle, its dwelling place. In this view the subject owns the body and can dispose of it. Considering the body as property easily involves an objectification and instrumentalisation of the body by the person himself which in the longer run could make him vulnerable to pressure by others to objectify and commodify his body.[174] One step further along this line is to consider the human body as

168 Resnik D. The commodification of human reproductive materials. Journal of Medical Ethics, 1998; 24: 388-93

169 Radin M. Contested Commodities. Cambridge, MA: Harvard University Press, 1996

170 Radin M. Market-Inalienability. Harvard Law Review, 1987; 100: 1849-1937.

171 Nussbaum M. Objectification. Philosophy and public affairs, 1995; 24: 249-91

172 Kymlicka W. Rethinking the family. Philosophy and public affairs, 1991; 20: 77-97

173 Radin M. Market-Inalienability. Harvard Law Review, 1987; 100: 1849-1937

174 Kant I. Lectures on Ethics. 1930

the sum of its marketable anatomic parts.[175] In some countries this attitude expresses itself in the exploitation of poor people who are encouraged to sell their body parts, e.g., blood and kidneys, for money. In addition to being ethically problematic in itself, it can undermine the voluntary donation of tissues. Currently, in most countries people receive financial compensation for donations to cover direct expenses and sometimes as a small gratification. Richard Titmuss suggested that allowing commercialisation of blood products, tissues and other body parts could reduce these to mere commodities which could undermine voluntary donation and lead to a reduction of the supply from donors.[176] If proven true this would underline our idea that such a commodification does not do justice to the full experience of human beings with respect to their bodies.[177] As we have argued above the body is to be considered an essential constituent of the individual and not merely as an instrument or vehicle the individual possesses. The relationship 'I have a body' should not be overemphasised at the expense of the relationship 'I am my body'. What is done to the body always concerns the person, directly or indirectly in a symbolic way.

Thus, what is disturbing about commodifying a human being is not so much the exchange of money in itself as is the notion that a subject, a moral agent with autonomy and dignity, is being treated as an instrument to fulfil the needs or desires of others. Considering the body as a commercial resource or product may lead to a demeaning of human life in society and could facilitate a tendency to sacrifice some human beings in order to obtain great benefits for many others. This may not seem likely now, but in our view it would be ingenuous to presume it may not happen in modern society with its emphasis on individual autonomy. But precisely this emphasis may facilitate such a tendency since it implies that those who are no longer and never will be autonomous again have lost an essential human characteristic and with it part of their dignity. We reject this view. Human dignity is inherent to every human being and requires that each human being be treated as a unique individual having incommensurable value. That is why any acceptance of trade in human body parts and of patents related to the use of body parts should be at the least carefully regulated.

Informed consent and use of body parts

European regulations

In contrast to the USA the notion of property rights in Europe is not used in regulations aimed at protecting the human body and its parts against abuse by others. There seems to be a general aversion to conceptualising body parts in terms of property. In Europe the predominant view is that the living body should not be considered as a legal object that can be owned, and in legal discourse property is in general not seen as a legal option to achieve protection

175 Cunningham PC. Is it right or is it useful? Patenting of the human gene, Lockean property rights and the erosion of the Imago Dei. Ethics & Medicine 2003;19 (2):85-98

176 Titmuss RM. The Gift Relationship - from human blood to social policy Vintage Books, Random House, NY: 1972, 198-9.

177 Toombs S Kay. The meaning of illness. A phenomenological account of the different perspectives of physician and patient. Kluwer Acad Publishers: Philosophy & Medicine, 1993; 42: 51-88.

of the body and body parts.[178] The Convention on Human Rights and Biomedicine of the Council of Europe states in article 21: "The human body and its parts shall not, as such, give rise to financial gain".[179] This is a broadly accepted document in the European context. We think good ethical reasons exist for this provision. Our observations on the meaning of the body in human existence are a prima facie not consistent with a view of body parts as mere material objects that as simple pieces of property can be owned, bought, sold or commercialised.[180]

In Europe regulations of the use and control of body parts removed from the body are rather based on rules derived from an extension of the concept of informed consent. Article 22 of the before-mentioned Convention establishes that informed consent is required for storing or using a human part for a purpose other than for which it was removed in medical intervention. Thus, the legal provisions for informed consent do not only apply to the taking of any tissue from a competent adult, but also revolve around perceived rights to control the possession, use and ultimate disposition of extra-corporeal organs or tissue. Informed consent grants the donor not only the right to set the initial limits of permitted use, but also to sanction any deviation from such initial permitted use.[181] It provides the individual with discretionary power over his body parts. Such use of informed consent is based on the concept of the integrity of the body which in turn can be founded on the philosophical notion of self-possession. Self-possession is one of the essential dimensions of personhood: the human person as a rational being 'possesses' himself.[182] Man, to a certain extent, is expected to govern himself. The operationalisation of this concept for legal discourse is self-determination. Self-determination must be distinguished from ownership. Ownership refers to objects and wealth that are the property of the owner. The human body and parts of it are not legal objects, but form an integral part of the human being as a legal subject. In legal discourse the human being is unthinkable without its body. Thus, the concept of property is not suited and not meant to define the human being in its material manifestation, the body. Law clearly distinguishes between property damage (damage to an object) and maltreatment (damage to a human being).[183] This distinction is also clear in European regulations. For example, the European Convention for the Protection of Human Rights[184] protects the right to liberty and security in article 5 and the right to private and family life in article 8. These articles do not deal with property. In contrast, the right to property is mentioned in article 1 of the First Protocol of this

178 Legemaate J. 'The Personal Cell Bank': juridische aspecten. Tijdschrift voor Gezondheidsrecht 2003;4:244-5

179 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Art. 21. Council of Europe, Oviedo, 4.IV.1997.

180 Stempsey WESJ. Organ markets and human dignity: on selling your body and soul. Christian Bioethics, 2000; 6(2): 195-204

181 Beyleveld D, Brownsword R. My Body, My Parts, My Property? Health Care Analysis, 2000; 8: 87-99

182 For those who adhere to one of the main religions in Europe, Christianity, Judaism and Islam, this is only the case at the level of social relations and interactions, since ultimately the human being is believed to belong to the Creator.

183 Leenen HJJ. Handboek Gezondheidsrecht, rechten van mensen in de gezondheidszorg. Alphen aan den Rijn: Samson 19882.

184 Rome, 1950, lastly amended 1 November 1998.

Convention. This article deals with objects of property and with different kinds of contracts related to property or income.

At the same time, the right to informed consent is deeply entrenched in European regulations. We already mentioned Council of Europe's Convention on Human Rights and Biomedicine,[185] article 22. Free and informed consent as a manifestation of respect for physical and mental integrity is also mentioned in article 2 of the Charter of Fundamental Rights of the European Union.[186] Also of particular interest is the adoption by the European Parliament of a series of amendments of the proposal of the European Commission on the use of human tissue and cells.[187] In the amended article 1 this proposal states: "…The human body cannot be the subject of property rights".

Thus, in the European context protection of discretionary power on body parts by the subject from whom they are taken is rooted in the right to protection of the integrity of the person and of the principle of respect for self-determination. This corresponds to the view that the body is integral to the human person.

It remains to be answered whether any exchange of money and any form of property rights is always wrong in the context of the donation and use of body parts. The next section will deal with this question.

Trade and compensations

Two forms of financial interests are mentioned in the question: direct payments for body parts and property rights on body parts. In this section we will deal with the first problem. The second is dealt with in Chapter 4.

We want to answer the question about the legitimacy of payments for body parts by referring to the Additional Protocol to the Convention on Human Rights and Biomedicine, on transplantation of organs and tissues of human origin.[188] This protocol, in addition to provisions on informed consent, contains some provisions that are important in this respect. Article 21.1 states: "The human body and its parts shall not, as such, give rise to financial gain or comparable advantage" Article 21.2 requires the prohibition of any advertising in the context of organ or tissue transplantation. And article 22 asks for the prohibition of trafficking of organs and tissues. Thus, this protocol clearly aims to exclude trade in human organs and tissue.[189] This is based on the principles that are laid down in the Convention itself (cf. note 59). We consider this

185 See note 59.

186 Nice, 7 December 2000

187 Report on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (COM (2002) 319). Document A5-0103/2003

188 Council of Europe, ETS. No. 186, Strasbourg, 24 January 2002.

189 It should be noted that in article 2 the protocol explicitly excludes (1) reproductive organs and tissue, (2) embryonic or foetal organs and tissue, and (3) blood and blood derivatives from the proposed regulations, because these are subject to other regulations, but cells, including haematopoietic stem cells, are included.

consistent with the view of the human being and the body presented in this section.[190]

However, in the same article 21.1 mentioned above it is made clear that the prohibition of financial gain should not prevent certain payments in the context of organ or tissue donation, in particular compensation of living donors for the loss of earnings or other expenses related to the organ or tissue removal, and payment of a fee (to the health care providers) for medical services and compensation in case of undue damage. In our opinion this exchange of money can be justified by pointing out that it does not constitute a payment for the donated body parts and that it is reasonable to compensate the donor for losses suffered because of the donation. This payment is, therefore, not a form of commodification of body parts but could instead be seen as a token of appreciation of society for the donation. Health care should be a public service equally accessible for all who need it, that is furthered by the participation of all patients who donate some tissue or participate in medical research. It should not become the scene for negotiations about payments for body parts or substances.

A different problem is raised by the fact that institutions and companies sell blood products and cultivated cells derived from tissue obtained from a patient to other research or health care institutions. They try to make a profit with it. Is that ethically justifiable? An extensive treatment of this question is beyond the scope of this chapter and we will only make a few remarks.

First, that which is sold and bought is not the tissue or organ itself as obtained from the patient but a derivative. Some processing has been realised. That those who did this get financial reward for their work is reasonable; it does not involve a direct commodification of body parts as such. Once the tissue or body parts are separated from the individual the boundary between those body parts and the individual person is blurred. They do not share the same dignity or the same protection as when these parts still formed an integrated whole in the person's body. Thus, a limited degree of commodification can be acceptable. It becomes more problematic when it involves cells or substances still closely connected to the original tissue and the profits become more substantial and go to private companies or persons. In our view it is recommended that such business be put in the hands of not-for-profit corporations that use their profit to further a public service. This counteracts a development towards further commodification of human body parts.

Second, we want to point out that objects of property can be valued not only for their extrinsic value (in the sense of market value) but also for their intrinsic value or for both. An example of the first is a businessman who values his stock of transistor radios, a clear example of a commodity, because of its market value. An example of the second is a personal letter from a grandfather in specific circumstances. Unless the author or the addressee has (had) an important public function it will not have extrinsic market value. Certain family possessions, like a painting, can have both an intrinsic value for the owner and an extrinsic value. This demonstrates that there can be reasons to treat an

190 The selling of hair that apparently is allowed in many countries can be considered as an acceptable exception since the cutting of hair is not invasive nor life threatening and does not involve any health care facility.

object as having intrinsic value even though it also has a market value. A change of ownership of such objects can happen without any exchange of money, as an expression of appreciation or of a special relationship. But, as we already saw, even a certain financial recompense or payment of costs for receiving such an object with intrinsic value need not be a commodification of the object. As explained above (section 3.3.2) full commodification means complete lack of subjectivity, complete instrumentality and fungibility. Human cells, even in cell or tissue culture, are never completely without subjectivity since they are derived from that person, and never completely fungible since they continue to bear the mark of the gift character of the donation. But it is also clear that to the extent that the cells or substances are only remotely related to the original donation and can in principle be produced in limitless supply, the product takes on more of the character of a commodity. The corrupting influence of money in the use of human material can be avoided if it is regulated by laws that promote non-market values such as human dignity, safety and welfare.[191] Suggestions as to the way in which this could be pursued are given in the chapter on patenting (see chapter 4).

4 MORAL ISSUES RELATED TO THE USE OF STEM CELLS FROM DIFFERENT SOURCES

Main problems and main principle

The main specific ethical challenges associated with human stem cell research are related directly or indirectly to the sources from which the cells are obtained. But there are also ethical concerns related to consequences in the sense of harm to possible donors of adult stem cells and to patients to be treated with some kinds of stem cells, as well as consequences for society at large. We discuss the main ethical issues related to research on stem cells obtained from different sources.

The main principles with respect to medical research involving human subjects are laid down in the Helsinki Declaration.[192] From this Declaration it is absolutely clear that the life and health of a research subject should always have priority over scientific progress that may result from the research. Some of these principles are elaborated in the Convention on Human Rights and Biomedicine of the Council of Europe (cf. note 59). Article 16.2 of this convention states: "the risks which may be incurred by that person are not disproportionate to the potential benefits of the research". This article refers to competent subjects. For incompetent subjects the rules are much stricter. With respect to human embryos the convention states in article 18: "1. Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo. 2. The creation of human embryos for research purposes is prohibited." (cf. § 2.2). This means that the convention distinguishes between research subjects after birth and embryos. This obviously is already a

191 Radin M. Contested Commodities. Cambridge, MA: Harvard University Press, 1996

192 World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Latest amended in Edinburgh, 2000.

normative decision. But even so the Convention requires protection of the embryo.

We will deal with the implications in discussing the different sources of stem cells.

4.2. Embryonic stem cells

4.2.1. Introduction

Despite very promising advances made with adult stem cells, the prevalent opinion among researchers seems to be that adult stem cells cannot entirely replace either ES and EG cells because much basic research remains to be done in the area of early human embryonic development.

ES research, like other research in which embryos are destroyed, differs from other medical research in that it requires the deliberate destruction of nascent human life to obtain research material. Stem cells are obtained by removing the inner cell mass of an embryo, thereby destroying the embryo. An attempt is then made to cultivate the cells. Thus, research with embryonic stem cells poses an ethical paradox. On one hand, the potential benefits from this research to human health seem to raise a moral imperative to promote it. On the other hand, this research is ethically objectionable because it involves the use, production and ultimate destruction of human embryos, causing harm to human dignity (cf. § 2 supra). It involves a conflict of competing concerns and priorities, each in the service of human goods and each driven by a desire to improve the human condition and to protect essential principles. Here, the need and desire to relieve human suffering caused by injury and illness can conflict with the widely shared desire and the ethical imperative to respect and protect human life.

The central ethical concern is whether the potential benefits of research, such as medical progress in treating diseases and prolonging the life of individuals affected by degenerative diseases, can be considered sufficient moral justification for the destruction of this nascent human life. This concern is complicated by the fact that it remains uncertain whether the research will in fact produce the hoped for benefits and whether other promising and morally non-problematic approaches may achieve comparable benefits.

A second ethical question rising from embryonic stem cell research is whether it is morally permissible to utilise stem cells obtained from embryos in a situation in which the embryos are not destroyed. This question can be answered via the same kind of ethical evaluation based on weighing risks and benefits as just indicated.

To determine the ethical acceptability of ES cell research we first have to consider the moral status of the embryos from which the cells are harvested. As explained in paragraph 2 we believe that the human embryo as a human being deserves full protection. This means that no normal embryo may be intentionally destroyed on behalf of any other human being and less so for research of which the benefits are still unclear and uncertain. Considering the human embryo a human being means that in our opinion the Helsinki Declaration and the before-mentioned Convention should also be applied to

research involving embryos. Hence, only if the source from which stem cells are harvested need not be considered a (developing) human being may the potential therapeutic benefits of embryonic stem cell research justify the use of these cells.[193]

We also wish to point out here that if one does not accept that the human embryo should be seen and treated as a full human being since we do not and cannot know whether it really is, there are still reasons to reject destructive embryo research. Prudence dictates that we consider the possibility that it is a human being and should not be deliberately destroyed. Or one could hold the view that simply being a member of our species, which the embryo doubtlessly is whatever one may think of it otherwise, is sufficient reason to grant it special protection. In fact, we cannot read article 18.1 of the before-mentioned Convention without understanding that it rejects the deliberate destruction of embryos. Would it not be ironic if that article had to be read as "whenever one performs embryo research the embryo should at least be killed respectfully".

In fact, there are three main sources of embryonic stem cells and each presents its own controversial ethical issues.

4.2.2. Surplus IVF embryos

The most readily available source of stem cells is surplus embryos that are a by-product of IVF techniques. These embryos include embryos of poor quality due to chromosomal abnormalities that make them inappropriate for transfer, and those remaining when couples who donated the gametes no longer need them for procreation.

An important aspect in the case of IVF embryos is the concept of the potentiality of the embryo to develop into a fully human being. This is complicated since the embryo cannot actually develop into a human being without being implanted in utero by medical intervention. Furthermore, many IVF embryos (probably roughly 50%) do not survive after uterus implantation for failure to nidate in the woman's uterus.[194]

Since IVF embryos are formed by the union of ova and sperm just like naturally conceived embryos and have started normal embryological development, they have the same intrinsic potentiality as in vivo embryos. This is potentiality in the sense of 'can develop as'. The position that extra-corporeal embryos are only special cells that acquire the potential to develop into an individual organism after implantation in the mother's womb, only attributes to the

193 Of course we realise that in most European countries (and elsewhere) induced abortion is accepted under certain conditions, implying the acceptance of a lower moral status of prenatal human life. We do not want here to repeat the abortion discussion, but want to point out that legalisation of abortion does not mean it is no longer an ethical problem and that abortion is generally justified by a conflict of interests in which the law accepts that the immediate need of the pregnant woman can overrule the protection of that foetus. For embryos in vitro such an immediate conflict of interests does not exist. So even acceptance of abortion does not logically imply acceptance of destructive embryo research. When it comes to the creation of embryos for research or to research cloning several additional arguments come into play (see further text).

194 ER Norwitz, DJ Schust, SJ Fisher. Implantation and the survival of early pregnancy. Review. New Engl J Med 2002;345 (19):1400

potentiality of these embryos in the sense of 'could become' (cf. § 2.3.2). We think this based on a misunderstanding of the intrinsic potentiality of the embryos. The in vitro embryo need not undergo any fundamental transformation as an entity to acquire the ability to go through the normal human life cycle. It has that intrinsic capacity. The fact that embryos created outside their natural environment are limited in their natural capacity to develop into a fully human person does not affect their inherent active potential to develop as a fully human being when implanted into the uterus. The fact that they cannot survive outside the uterus does not indicate a lack or loss of this potentiality. Thus, there are no reasons why in themselves the in vitro embryos would have a lower moral status than embryos conceived in vivo and embryos implanted in the uterus. Furthermore, these embryos have been created intentionally outside the womb by human action, giving the agents a responsibility for them. All newly formed embryos can only develop inside the womb of a woman and there is no reason why certain external conditions for growth would be required to grant the human being normal human status in this early stage of life.

The proposal that a human embryo does not have full human status because it is dependent on the mother for its development leads to unacceptable conclusions. For this would mean that a foetus would not only not have full human status until viability, but even a newborn baby would not have such status since it is dependent on the care of others. In particular, premature babies would not deserve full protection because they are dependent on intensive care. Since this conclusion is unacceptable we reject this kind of reasoning.

Changes in the intricate interrelations between mother and unborn child should not be viewed as alterations of the child's moral status, but as part of the ongoing epigenetic process all along the continuum of natural development that begins with conception and continues into infancy.

Arguing that IVF embryos lack the immanent potentiality for maturation and development into a foetus is self-contradictory with the aim of the in vitro fertilisation technique itself. IVF is a reproductive technique developed to allow a woman to conceive and bear children of her own and her partner's genetic makeup. Nobody doubts whether the 'product' of in vitro fertilisation has the internal potential to develop into a child when the right external conditions are given. The observation that a lower percentage of IVF embryos is able to implant into the uterus than naturally conceived embryos may be due to abnormalities in the embryos themselves (e.g., chromosomal defects) or problems associated with the culture conditions. It cannot in itself constitute a reason to subject embryos to a treatment with high mortality. A natural course of events can not in itself constitute a moral reason to act in the same way. The purpose of medicine is to restore nature where it fails. Diseases occur in nature, but are a deviation from what is considered normal and do not provide a reason to intentionally make people ill.

Intention and utility

These observations also lead to a rejection of the view that the moral status of an embryo depends on the intention of the persons who brought it into being. As long as their intention is to have a child, then that embryo should be protected. But if that is no longer the intention the embryo will not be transferred to the womb and therefore has no chance of survival, thus losing its moral status according to this view.

We readily admit that relations are important for human existence and development. But in normal social life this never leads to the conclusion that a single lonely person would not be fully human or deserve full protection. So why would the status and protection granted to an embryo depend on a relation with other persons, or on the intention of others to have the embryo develop and be born as a baby? The intention of others does not change the embryo itself nor its intrinsic potentiality ('capacity to develop as') and there is no reason to propose a change in moral status. A newborn baby cannot survive without care by others, but that does not mean it has a lower moral status if nobody intends to care for it. We would rather argue that the relationality of human beings implies a responsibility for others that increases with the vulnerability of a member of the human race.

An additional argument is often put forward with respect to surplus embryos whose parents do not want to use them for having children or donate them to other couples. These embryos will never be implanted into a uterus and are destined to die. Using them for research, out of which some good may come, could be considered as a relatively dignified and respectful alternative that should be ethically acceptable, according to this reasoning. Some may even argue that such use is morally imperative. In answer to this we want to emphasise that we are not free to pursue good ends by unethical means. There is no ethical way to deliberately destroy the life of some humans in the hope of benefiting others through furthering scientific knowledge. Not being able to save embryos from the dead is one thing –a situation that has been brought about deliberately. Intentionally causing their death is another. Even if the death of an individual is believed to be otherwise imminent, the intentional killing of a human being for the alleged good for other human beings is wrong, even if it potentially offers great good to those who are suffering. Not only should the major objective of medical research be saving lives, the procedures by which this objective is pursued should also respect life. Not only the goals, but also the means should be ethically acceptable (cf. § 1.4).

The ethical dilemma of ES cell research is complicated by the fact that the medical benefits of ES cells have not yet been scientifically demonstrated. The results with alternative methods suggest that the destruction of human embryonic life is not necessary for medical progress (cf. Chapter 2 of this report). This poses the question whether the research proponents are objectively considering all available options and routes to accomplish the same goal or are merely claiming the use of embryos to get stem cells just because they are available and form a scientifically interesting object. On the basis of the principle of subsidiarity the ethically less problematic alternative should be preferred (see § 1.4 and also below § 4.3).

Consent

The use of embryos remaining from infertility procedures requires that the couple, or at least the woman, give free informed consent.[195] Consenting in stem cell research raises special questions such as whether it is possible to adequately inform the donors of the possibility of creating immortal cell lines, of the possibility of commercialisation of scientific discoveries that might result from their donation and of the implications that donating genetic material may have for donor privacy. Another important ethical issue in this context is that some couples may feel that they cannot refuse when their doctor (the key person to become parents) asks permission to use their excess embryos for research purposes. In other words, can coercion, subtle as it may be, be avoided? As embryos become valuable to biotech companies as sources of cell lines, doctors may increase the dose of fertility drugs in order to produce more 'excess' embryos in the hope that some of them might eventually be donated for research. The fertility drugs given to a woman to produce extra cycles of ovulation can increase her risk of diabetes, blood clots, heart failure and even death.[196]

4.2.3. Embryos created for research

In this case the ES cells are obtained from embryos intentionally created for that purpose by IVF. Just as in the case of IVF surplus embryos a central moral issue is the moral status of the embryo. But embryos produced for research raise this question in an even more poignant way. To decide to create nascent human life expressly for the purpose of experimentation and use is to cross another significant moral barrier. It is one thing -also for those who oppose it[197]- to conduct research on surplus embryos from IVF procedures, but another thing to create embryos solely for research purposes in which they will be destroyed. They are created as laboratory materials and are used in a way that is incompatible with their human dignity. On the basis of the arguments put forward in the previous paragraph we conclude that embryos produced for research purposes do not in themselves have a lower moral status than embryos produced for fertility treatments. The reason for which the embryo has been brought into being, reproductive purpose or source of cells, does not affect his status as human being, just as a child born as the result of rape has no lower moral status than a child conceived in love.

We want to stress that the previously mentioned article 18.2 of the Council of Europe Convention on human rights and biomedicine explicitly asks to prohibit the creation of embryos for research.

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195 Stem Cell Research and Applications. Monitoring the frontiers of Biomedical research. Report of the American Association for the Advancement of Science and Institute for Civil Society. (November 1999).

196 Financial incentives in recruitment of oocyte donors. The Ethics Committee of the American Society for Reproductive Medicine. Fertil Steril, 2000; 74(2): 216-220;

197 Since IVF clinics produce more embryos than they are likely to use, knowing that some will probably be destroyed, the moral responsibility for production, use and destruction of surplus embryos is no less than for deliberate production for use and consequent destruction.

4.2.4. Clone embryos

In the first instance embryos created through somatic cell nuclear transfer (SCNT) would pose the same concerns as embryos obtained by in vitro fertilisation procedures solely to be used as research objects. The embryo produced by cloning and not by the fertilisation of an egg cell indicates that it is different in its origin from a normally conceived embryo. But as we saw, the way in which an embryo is brought into being does not in itself affect its moral status. However, it should also be recognised that, in addition to the biological concerns, there are philosophical, anthropological and social concerns related to the status of the cloned embryo that make cloning even more ethically problematic.

Since the cloning technique, in which somatic DNA is transferred to an enucleated egg, does not involve fertilisation of a female by male gametes, it hinges on the question of whether the clone should be characterised as a human embryo or as a clump of growing cells with no moral significance. The presence of a normal human genome in the cells that constitute the cell cluster is not sufficient for claiming that there is a human being. All the cells of the organism have the same DNA and are able to multiply to produce a cluster of cells when the right culture conditions are given, but they are not regarded as having the same moral status as an embryo.

At issue here is once again the natural or real potentiality of the clone to become a full human being. On the basis of results obtained so far with animals it must be expected that if performed with human cells the cloning method restores the somatic chromosome number and initiates the production of a blastocyst-stage embryo genetically identical to the nuclear donor. The initial product of SCNT is not only an actively (growing) cell, but an active egg cell that is capable (in animals) or may be capable (in humans) of developing as a new specimen of the species. The processes of cellular growth and differentiation into the tissues and organs of the developing organism are co-ordinated by the cell's genetic material supported by the cytoplasmic environment of the egg cell. Thus, since it satisfies the two most important elements in the definition of a fertilised egg cell, the result of SCNT is a living cloned human embryo. The immediate intention of the SCNT is precisely to produce just a human embryo capable of developing as a human embryo, at least for the early stages. Although the product of SCNT lacks the natural bi-parental precursors and is produced by human artifice, neither its artificial origin nor its uni-parental source alters the decisive point. Scientific evidence with animals shows that this entity in principle has the capacity of developing into all the later stages of the organism, even though the success rate for all cloning attempts is very low. So far it has not been scientifically demonstrated whether a human clone embryo has the real potential to develop to term when implanted into a uterus.[198] Yet the clone embryo is an entity that is the first

198 The claims of Clonaid of the Raelians that announced the birth of the first cloned baby Eve at Second Christmas day 2002 has not been scientifically proven. Some researcher say that the technique that is used so far to clone animals will not work for humans; see: Pearson H. Human clones doomed? Current technique may scupper key primate egg proteins. Nature Science Update, 11 April 2003, http://www.nature.com/nsu/030407/030407-12.html

stage of a developing organism of the human species with a full genetic complement and its own individual genetic identity that deserves, on biological grounds, to be called an embryo.[199] A supporting observation is that nature shows that fertilisation is not the only way to initiate a new individual of the species. Identical twins are the result of one fertilisation that gives rise to two conceptions and two individuals (cf. § 2.4.3).

Reproductive and 'therapeutic' cloning

Based on different goals a distinction has been made between reproductive cloning, with the ultimate goal of producing a child, and cloning for biomedical research with the purpose of using the embryo in research or for extracting its stem cells for developing cures for human diseases. (In literature the latter is often called therapeutic cloning; we will rather speak of research cloning.)

First of all, we want to stress that the rejection of reproductive cloning and the judgement that research cloning is less problematic does not in itself morally justify the latter. For determining the ethical value of research cloning we also have to look at the morality of the cloning itself and not only at the goals and consequences. Since the result of cloning is the production of one or more embryos that are genetically (near)[200] identical copies of another individual, all types of cloning should be considered as a reproductive action, independent of the goals that are pursued and of the stage to which the cloned embryo is allowed to grow. Both cloning to produce children and cloning for biomedical research begin with the same act of cloning and with a newly created human embryo. Both involve deliberate (genetic) manipulation of human life and the deliberate production of genetically (near) identical human beings. Consequently, both imply an instrumentalisation of some human beings for the benefit of others that constitutes an abuse of biology and medicine.[201]

Cloning to produce children would amount to manipulative manufacturing of humans. It would 'make' children that would be burdened by specific expectations that would frustrate their free acceptance. Given the high risk and mortality grades in the cloning of other mammals we are of the opinion that it is extremely unsafe, and research with humans in order to discover whether it can become safer would be ethically unacceptable.

Cloning for biomedical research raises more controversial ethical issues. First, the act of cloning embryos may be undertaken with healing motives, but it is not itself an act of healing or therapy. The benefits of any such acts of cloning are at the moment hypothetical and will only be substantiated in the future, if at all. But even if those medical treatments will eventually succeed it is critical to recognise that the cloned embryo will not itself be the beneficiary of any therapy as, much to the contrary, obtaining the stem cells necessarily results in his or her destruction. Just as in the case of IVF embryos created for

199 Although the clone is genetically virtually identical to the individual that was the source of the transferred nucleus, there may be imprinting or epigenetic reprogramming differences in gene expression

200 The donor of the cell nucleus and the clone will differ in mitochondrial DNA that comes from the donor of the egg cell. This comprises only a very small percentage of the total DNA in a cell.

201 Council of Europe. Convention on Human Rights and Biomedicine 1988: Additional Protocol on the Prohibition of Cloning Human Beings.

research, it requires the deliberate production, use and destruction of cloned embryos, that are not different from those that could be used in attempts to produce cloned children, only for research purposes, and in this case in order to develop genetically personalised therapies for each individual patient.[202] Thus, this so-called therapeutic cloning would involve people having a clone made of themselves in the embryonic stage that will be completely instrumentalised for their own health.

The therapeutic interest in cloning arises largely in response to a chief obstacle encountered by scientists doing research on embryonic stem cells, namely, the immune rejection of transplanted cells or tissue derived from ES cells by the patient. Since cloned embryos would be genetically identical to the patient of whom it would be a clone, cells derived from such clone embryos would not be rejected by the patient.[203] Furthermore, some scientists believe that stem cells derived from cloned embryos of patients might prove uniquely useful for investigating and possibly treating many genetic diseases and disabilities, providing aid and relief to millions. However, this is quite uncertain at the moment.

Furthermore if research cloning would become medically successful, it would pose another tremendous problem. This is the need for astronomic numbers of egg cells. If successful the method could be applied to millions of patients with different degenerative diseases like diabetes, Parkinson, Alzheimer dementia etc. However, to make a usable clone for every patient would require at least about 100 egg cells for each patient. Altogether this would result in a demand for millions of egg cells. This would lead easily to exploitation of woman to donate their egg cells for money (cf. note 42 supra). Another reason why this is not the way to go. This could change, however, if the amazing recent finding that mouse ES cells in vitro can produce egg cells (oocytes),[204] can be repeated for human ES cells and those oocytes can be fertilised and form a normal embryo. Large scale in vitro production of egg cells could then become feasible.

Developing new therapies for patients is definitely an admirable objective that in general deserves support of society. But against the technique of 'therapeutic cloning' we have the same objections that have previously been put forward against the production and use of embryos for research to develop treatments (see § 4.2.2 and 5.1). Furthermore, there are other morally unproblematic ways for solving the immune rejection problem and achieving similar scientific results, such as the use of adult stem cells isolated from the patient (cf. Chapter 2).

202 Robert P. Lanza, Ho Yun Chung, James J. Yoo, et al. Generation of histocompatible tissues using nuclear transplantation. Nature Biotechnology 2002; 20: 689-96.

203 Whether that in fact will be the case is still uncertain: Rideout III WM, et al. Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy. Cell 2002; 109: 17-27.

204 Hübner K,Fuhrmann G, Christenson LK, Reinbold R, De la Fuente R, Wood J, Straumss III J, Boiani M, Schöler HR.. Derivation of oocytes from mouse embryonic stem cells. Science 2003; 300: 1251-6

4.3. Foetal stem cells

In the first place it should be pointed out that only very limited positive and some negative medical results have been obtained so far.[205]

The use of foetal tissue obtained from elective abortions requires the ethical acceptance of abortions performed for reasons that are entirely unrelated to the research objectives. But although the researchers who will use the foetal tissue are not responsible for the death of the foetus, it is difficult to separate this research from the problem of abortion. Before an abortion takes place, researchers will inquire about the availability of the foetus that will be destroyed. Appointments have to be made at the time of the abortion and the 'harvesting' of the tissue. The timing of the abortion is in due course likely to be influenced by the wishes of the researchers with respect to the age of the foetus. Harvesting the foetal tissue, like EG cells for research, implies at least a tacit support of the abortion and the removal of the tissue. Hence, scientists using foetal cells, i.e., EG cells, from induced abortion for research purposes place themselves in moral complicity with abortion providers which makes their research ethically problematic.

Furthermore, the possibility of donating foetal tissue for medical use and even more, the possibility of receiving money for it, just as for egg cells, could influence the decision to undergo an abortion, thus encouraging the current abortion practice.[206]

The use of cells isolated from foetuses also raises questions of informed consent similar to those raised by donated embryos. In the first place one may wonder whether the parents will really understand what it means to donate foetal tissue to science. But even more important one may wonder whether parents who just decided to have their unborn child aborted can be considered as proxy's acting in the best interest of their foetus who can give an ethically and legally credible informed consent.

The use of cells from miscarriages is in principle ethically acceptable when the normal requirements for such research, in particular the informed consent of the parents, are observed. Practically this will often be problematic, but not necessarily impossible.

4.4. Adult stem cells

The use of human stem cells obtained from sources such as adult blood, bone marrow and nerve tissue, and umbilical cords and placentas, raises no new ethical issues compared to those of research with human subjects and with organ donation. Since these cells require neither dedifferentiation nor the destruction of human embryos, they are not controversial. Additionally, the

205 Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001;344 (10): 710-9; Greene, PE, Fahn S. Status of fetal tissue for the treatment of advanced Parkinson disease. Neurosurgical Focus 2002;13 (5):article 3.

206 Jimenez M. US investigates traffic in fetal parts. National Post, November 27, 1999

promising work being done on adult stem cells eliminates the need for embryonic stem cell research and makes it unjustifiable.[207]

An essential requisite for ethically legitimate research is that the researchers must obtain free and informed consent from the donor and the eventual receiver of the cultivated cells or tissue. Informed consent includes the potential donor receiving correct, realistic, understandable information about the possible risk to health and the real benefits of the research. Research in this field will be subject to existing legislation on medical research involving human subjects. We will not further discuss this here since this concerns a well-regulated field.

4.5. Ethics of parthenogenesis

Some claim that producing embryos by parthenogenesis could solve ethical problems surrounding embryonic stem cells. This is by no means clear. The mere fact that such an embryo is not likely to be viable does not mean that it removes all ethical concerns. Animal studies of parthenotes have shown that they, in the early stages of development, can develop similarly to normal animal embryos. However, when transferred to the animal uterus, few have reached the stage of implantation.

Recent research has made this question even more urgent. In the first place researchers have found that mouse ES cell cultures in vitro not only can produce oocytes, but even blastocyst-like structures, presumably by parthenogenesis.[208] And even more recently another group reported that from Macaca monkey parthenotes ES cell lines can be cultured that are able to develop into differentiated neurons.[209] So it seems that parthenotes could become sources for (female) ES cells. Whether those cells could be safely used for therapeutic reasons remains to be seen (cf. chapter 2 § 2.2.3.).

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207 See for compilation of research news and opinions on adult stem cells: http://www.stemcellresearch.org/ especially "Testimony before the House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources" of David A. Prentice, Prof. of Life Sciences, Indiana State University: Adjunct Prof. of Medical and Molecular Genetics, Indiana University School of Medicine, July 17 2001.

http://www.stemcellresearch.org/testimony/prentice3. htm

For example, Alan Trounson, Australian embryonic stem cell expert and a leader in the field worldwide, is reported to have said that stem cell research has advanced so rapidly in the past few months that therapeutic cloning is now unnecessary. Trounson abandoned his call for therapeutic cloning, saying scientific breakthroughs mean there is now no need for the controversial technique. Professor Trounson said therapeutic cloning faced logistical problems, and that other techniques were showing great promise and offered better options. "Stem-cell cloning not needed, says scientist", The Age (Melbourne), pg. 2, July 29, 2002; "Stem-cell research outpaces cloning", The Australian, pg. 3, July 29, 2002;

"Therapeutic cloning no longer necessary: expert", AAP Newsfeed, July 29, 2002

208 Hübner K,Fuhrmann G, Christenson LK, Reinbold R, De la Fuente R, Wood J, Straumss III J, Boiani M, Schöler HR.. Derivation of oocytes from mouse embryonic stem cells. Science 2003; 300: 1251-6

209 Vrana K, Hipp JD, Goss AM, et al. Nonhuman primate parthenogenetic stem cells. Published online before print September 22, 2003, Proc Natl Acad Sci USA 10.1073/pnas.2034195100

Just as in the case of cloning this technique once again raises the fundamental question of what it means to be human and the ensuing considerations of how human beings should be treated.

The moral status of the parthenote is not clear. Unlike the cloned human embryo the human parthenote has a mother but not father. The main question is whether this form of life should be classified as a defective human embryo or whether they are not real individuals of the human species at all but a biological artefact. If they are defective embryos, than they may pose at least as many ethical problems as other methods, including SNCT. But if, because of its origin and inherent defectiveness and incapacity to go through a normal human embryonic development the parthenote lies outside the moral community of the human species and can be classified as cellular tissue, then it could be a used as a source for embryonic stem cells, without specific ethical issues. In other words, do they have a 'can develop as' or a 'could become' potentiality? (cf. § 2.4.2.) An answer to the question of the question of the status of the parthenote requires experiments with animals. If in the animal world, including other primates, extensive experiments show that parthenotes can only realise a very limited embryonic development, we may well conclude that parthenotes are artificial entities that resemble early embryos but cannot be considered as individuals of the species and in the case of human parthenotes need not be protected as such. An essential element of the definition of an embryo is that it is an organism that normally under the conditions required for the organism at that stage, has the potential to go through a full embryonic development typical for that species. If a parthenote is right from the beginning structurally unable to develop as an individual of the species there is no reason to consider it as such. However as long as this is uncertain we should be prudent and do not create human parthenotes for research in which they are decomposed.

4.6. Hybrids

Experiments in which human somatic cells were fused with animal oocytes showed that they were able to develop to the blastocyst stage. Stem cells extracted from the blastocyst were demonstrated to be human stem cells and surprisingly, the mitochondria of the cells were also human in genotype.[210] However, there is insufficient scientific evidence about the status of this entity. Implantation into the uterus of a woman for gestation would be necessary to know whether the combination of a human cell and a non-human egg has the potential to become a living human being. Since this possibility cannot be ethically contemplated without a positive answer, in the face of our present uncertainty we include these biological entities in the category of cloned human embryos. Here also, scientific experiments with animals should clarify whether such an entity would have to be considered as an individual of the species or not, just as in the case of parthenotes.

210 Wade N. Researchers claim embryonic cell mix of human and cow. New York Times. November 12, 1998: A1

4.7. Moral status of stem cells

Experiments with embryonic stem cells isolated from mice suggest that stem cells cultured in the laboratory in a specific way tend to form an aggregate of cells capable of initial development into an embryo. Recent results also indicate that in vitro cultures of mouse embryonic stem cells develop not only oocytes but also blastocyst-like structures, apparently through parthenogenesis. Whether these really are parthenotes and are viable remains to be seen (see above). Nevertheless, such results raise the question about the moral status of stem cells. If stem cells can grow into a complete organism, then they should be characterised as embryos and consequently, research on such stem cells could itself involve the creation and or destruction of embryos. [211]

Whether stem cells should be characterised as embryos or as specialised body tissue hinges on an understanding of stem cells' potentiality. Since potentiality is being understood as natural potentiality, determining the moral status of stem cells rests in part on whether its potential to become a human being is natural or contrived as is the case with a somatic cell nucleus. At issue here is the question whether stem cells by themselves can develop as a human embryo without any process of activation that affects the transformation of the cell into a human embryo. The natural development of the individual cells of the blastocyst is to become parts of a human being. Isolated from the total structure of the embryo the embryonic cells, even under favourable growth conditions, will not develop the trophoblast or other structures needed for continued development. Experiments with mice suggested that stem cells could develop into all the parts of a living organism only when placed in placenta-like cells or in a trophocytic matrix to simulate the placenta-forming cells. If we consider the cells giving rise to the placenta as an essential part of the embryo we can conclude that even embryonic stem cells do not have the active capacity to develop into a human being. They would be potential embryos only in a passive manner (the 'could become' potentiality, cf. § 2.4.2) in a sense similar to sperm and egg cells.

The potential of embryonic stem cells to become a human being seems to be much more like that of a somatic cell that could be cloned than like an embryo. That embryonic stem cells probably can be induced to develop as an embryo with less laboratory manipulation than specialised adult cells does not indicate that they in themselves have a fundamentally different status from other somatic cells. The fact that human embryonic stem cells in culture, as well as adult stem cells, constitute a scarce resource entails the ethical duty to use them prudently and efficiently, like all scarce resources. But although embryonic stem cells as such do not possess a moral status that would oppose their use in research, the use of those cells raises an ethical problem in that they are derived from embryos destroyed in the process of obtaining them.

211 Hübner K,Fuhrmann G, Christenson LK, Reinbold R, De la Fuente R, Wood J, Straumss III J, Boiani M, Schöler HR. Derivation of oocytes from mouse embryonic stem cells. Science 2003; 300: 1251-6

4.8. Co-operation with a morally wrong act

Because in principle stem cells proliferate indefinitely, it should be possible for much clinically valuable research to be carried out world-wide on the directed differentiation of stem cells using the lines that have been derived so far.

This possibility raises the question of whether it is ethically justified for researchers who have not contributed to the destruction of an embryo or foetus to utilise stem cells obtained in these ways. Not all acts resulting from others' wrongdoing are unethical. Only in cases where the researcher is intentionally involved in performing the wrongdoing is the prohibition of co-operating with evil absolute. In other cases the morality results from a balancing of benefit and harm.[212]

Since the "material and methods" section of a research protocol is part of the whole experiment, ethical and scientific evaluation of an experiment must take into account both the methods and materials used in the research process. Therefore, the source of stem cells obtained for research is both a scientifically and ethically relevant consideration. Although researchers do not participate in the derivation of embryonic stem cells, as long as embryos are destroyed as part of the research enterprise, researchers using embryonic stem cells would be involved in the death of embryos since this is the only way to obtain these cells. In addition, embryonic stem cell research provides the very motivation for obtaining these stem cells and thereby destroying human embryos.

To prevent scientists from participating in stem cell research in which the cells are derived in an unethical way, documentation of the original source of the stem cells must be easily available to researchers and to patients who receive stem cell therapy.

5 COLLATERAL EFFECTS OF STEM CELL RESEARCH

For a correct and complete ethical evaluation of a way to proceed we cannot separate it from an ethical assessment of the effects that flow from it. After we have considered the morality of the different sources of stem cells, it is necessary to consider the moral consequences that approval or disapproval of this research may bring about for the well-being of society.

5.1. Ethical price of omission

Stem cell research also raises the question about the duty of society and biotechnology to those of its members who are suffering. Blocking important medical research has an effect on the lives of those who would supposedly benefit from its results. Thus, restricting ES cell research implies a responsibility for those patients who could possibly benefit from it. There is a

212 Smith RE. The principle of Cooperation in Catholic Thought. The Fetal Tissue Use: Medical and Ethical Aspects. Braintree MA: Pope John Center, 1994: 81-92

general social and political responsibility to take measures to alleviate human suffering. But this is not our only moral obligation. The duty to heal is a relative duty, meaning that it does not override all other considerations. To seek a cure for patients at the direct expense of others violates the social ethical principle of equal respect and protection for all individuals as well as the first principle of medicine to "do no harm". Improving health is not the only value in medical morality. As argued above, the deliberate (creation and) destruction of human embryos poses serious ethical problems.

Furthermore, the moral duty to take measures to further medicine also entails the duty to make efficient use of the available resources. Recent developments in adult stem cell research strongly indicate that this line of research is most promising in providing therapies in the relative short term. Thus, the principle of good stewardship also pleads for directing funds to that type of research and not to ES cell research. The observation that certain types of fundamental research (e.g., in developmental biology and the aetiology of diseases) are so far only possible with ES cells does not provide sufficient reason to override the strong ethical objections to it.

Devaluation of human life

Giving moral approval to embryonic stem cell research risks significant moral harm to our society by degrading the dignity and intrinsic value of each human individual.

Even if we do not view the human embryo as a "person" or an individual with a full set of human rights we must agree that an embryo is a form of human life in its beginning stages. Treating a (potential) human individual as mere raw material for satisfying our own needs is a violation of the respect due to mankind. It causes harm to ourselves and others. When some (potential) individuals are destroyed in the name of medical science, the promotion of patient welfare and total social good, the dignity of human being is assaulted. This is even more the case when embryos are created for research. The deliberate creation and destruction of human embryos solely because freshly created embryos might be superior for research purposes to those from a freezer is a manifestation of an utilitarian ethic which justifies treating nascent human life as a commodity to be manufactured, endorsing the complete transformation of nascent life into nothing more than a resource or a tool. Justifying this by referring to positive ends whose realisation remains uncertain involves dangerous ethical reasoning. If good ends would justify a lower degree of protection to some groups of beings that belong to mankind, the position of seriously damaged and vulnerable individuals of our species is threatened (cf. § 2.3.4). Any tendency in that direction should be withstood, and in particular in health care.

5.3 Manipulation of human life

Cloning of human embryos for research will open the door to additional moral hazards. It might facilitate reproductive cloning even if this would be prohibited. The prohibition of reproductive cloning and the acceptance of

research cloning would be problematic for two reasons. In the first place it would be difficult to control whether in a laboratory annex clinic cloned embryos would not be implanted into a woman because she wants a child and cannot get it otherwise. In the second place, it would lead to a bizarre situation in which the law would require all cloned embryos to be killed before they are born. In other words, the law would mandate the termination of pregnancies of such cloned embryos by abortion.

Finally, if SCNT turns out to be feasible for man the DNA of the transferred nucleus might be manipulated, raising the complex problem of inadvertent or deliberate germ-line intervention. This raises many other ethical issues upon which our society needs to reflect.

Thus, the central question raised by these developments is not just the status of the human embryo, but the meaning and purpose of human life. In the stem cell debate we are confronted with a crucial question that cannot be evaded and demands an unequivocal answer: does human life have an inherent value simply because it is human? The answer that our societies give -explicitly or tacitly- will deeply influence our culture

Pressure on woman

Another problem with ethical implications related to the production of embryos for research either by IVF or –and particularly- by research cloning is the need for egg cells. The extent of epigenetic reprogramming, which is crucial for successful cloning, varies from one cloning event to the next. Consequently, the biological properties of cloned stem cell preparations also vary. It may be necessary to produce and test multiple stem cell preparations before they can be used in transplantation therapies. In addition, cloning is an inefficient process requiring many eggs to make a single ES cell line. Thus, cloning for biomedical research will require an abundant supply of unfertilised eggs. In order to get them clinics or industries would offer money to women to donate their egg cells after induction of ovulation. In the USA women are already sometimes offered thousands of dollars for their eggs. Since ovulation stimulation and egg donation is not without risk, this would give rise to exploitation of women who would subject themselves to such treatment solely for the money. Informed consent may not be sufficient to prevent this because payment in a situation of need would frustrate a free decision.[213] Once this is accepted, social responsibility for the poor could be undermined since 'they can always get money by donating their eggs' (cf. § 3.3.1. of this chapter and chapter 4).

213 Lindheim SR, Chase J, Sauer MV. Assessing the influence of payment on motivations of women participating as oocyte donors. Gynecol Obstet Invest. 2001;52(2):89-92

5.4. Harm to biotechnology and medicine

Underlying questions about stem cell research lie major questions about the relationship between science and technology[214] on the one hand and society on the other. This is a complex issue in itself about which we will only make a few remarks from an ethical perspective.

It is important to distinguish between the responsibilities of the scientific communities and society at large as represented by its governments. The government should not prescribe how scientists should think, to what theories they should adhere and what methods should be used in their research. Politicised science is usually not the best science. The government has, in addition to a general task regarding universities as institutions for scientific education, at least two major responsibilities with respect to scientific research. First, it should decide on what kind of research it will spend public funds. Second, it should see to it, through adequate regulations and procedures, that the funded research respects fundamental social, legal and ethical norms. These tasks confront the governments, and society at large, with the task of balancing the freedom and creativity of scientists with the well-being of our society as a whole and of each of its members.

The first ethical obligation of researchers is to guarantee that scientific progress does not violate the respect due human dignity. The true dignity of biomedicine is of an instrument, directly or indirectly, to serve mankind. When its activities might undermine the respect due mankind in whatever shape or stage, its own dignity becomes threatened. Limitations on its activities and use of human subjects posed by ethical reasons are required to maintain biomedicine's true dignity. Scientific advance and medical progress in themselves are not the overriding human goods to which society should be committed. Research must be judged not only by the ends it serves, but also by the means it employs.

Furthermore, scientists have the responsibility to be truthful in speaking about possible therapeutic results from certain lines of research, i.e., ES cell and adult stem cell research. One of the problems of this whole issue is that many experts in the field have either personal or professional financial interests in one line of research or another This often makes it difficult to get a truly independent opinion on new developments and claimed results. In fact, we want to stress that governments have the responsibility to see to it that independent expertise is maintained.

Loyalty to the highest moral and human aspirations of science and medicine requires that we consider not only why and how to proceed with new lines of research, but also whether there are compelling reasons not to do so or respect certain limits. Scientific research cannot be weighed against the right to life of individuals; they represent different moral levels. As expounded before, society has profound reasons not to permit medical research that implies the destruction of human life in the name of possible benefits for others.

214 Science and technology represent different human activities. Science is meant to aim at the advancement of knowledge and insight in reality, technology at insight in the way in which we can intervene in reality and bring about new artefacts. But nowadays, especially in biomedicine and biotechnology these two are closely related and together have become an instrument to achieve goals set by the scientists themselves or, as is mostly the case, by those who finance them.

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Who owns my ideas about your body?

Steps towards a humane intellectual property regime for human stem cells and other human tissues

Dr Asher Meir

1 GENERAL INTRODUCTION

The scientific study of human stem cells, as well as other human tissue, bears great promise to benefit mankind, yet it also bears a great potential for irresponsible use of our unique human inventive gift. The challenge for our race is to effectively exploit the ability of this technology to alleviate human suffering and to advance understanding, while ensuring that scientific and commercial enthusiasm don't trample human rights and human dignity.

A surprisingly important focus of the ethical debate over stem cell research is the granting of patents for inventions in this area. The seemingly arcane and mundane topic of patents has played a central role in the ethical debate for two reasons: the influence of patents on the direction of research and development, and the powerful statement patents make about the extent of human mastery over their subject matter.

Patent law critically influences what kinds of research and development can attract private funding. In effect, patents are the fulcrum which transmits market forces to the research establishment. Without them, scientific innovation cannot be effectively translated into commercial success. It follows that subtle changes in patent policy can have an important impact on research agenda and research practices.

The direction of research has ethical importance both in terms of commission and omission. The patent regime should encourage the development and dissemination of treatments that improve the quality of life, without encouraging destructive research practices.

In addition, the entire concept of "intellectual property" is ethically charged, because intellect signifies transcendence, while property signifies limitation and exploitation. Intellectual creations, even more than material ones, are never created ex nihilo by the inventor; rather they are necessarily rooted in a general cultural inheritance. Furthermore, their abstract nature means that they can be enjoyed by all without detracting from the enjoyment of any. Giving an individual the right to appropriate the fruits of such creations certainly requires ethical scrutiny.

The ethical paradox of "intellectual property" is augmented when the subject of the patent is not a novel invention of the human mind but rather is based on human physiology, which is the common heritage of all mankind. Patents on stem cells could be interpreted as ownership and economic exploitation of mankind.

These considerations will guide us in envisioning what kinds of patent policy will best serve the ethical nature of mankind.

From a practical point of view, a patent regime should encourage the development of novel therapies to benefit the greatest number of patients, without inducing undesirable research practices that violate the rights and dignity of subjects.

From a cultural point of view, the patent regime should convey the impression that society is granting the inventor a limited economic right as an incentive for his effort, not lordship over a vital aspect of human knowledge and technology.

This paper will attempt to assess the extent to which ethical problems are present in current patent regimes, and to suggest practical ways of raising ethical standards in this area.

The first section of the paper is a general overview of what patents are and what kinds of ethical issues they raise. The second section discusses concerns arising from the way the patent regime impacts the conduct of research. The third section discusses inherent problems in granting property rights, including patents, in stem cells.

2 PATENTS AND THEIR ETHICAL DIMENSION

For hundreds of years, governments have granted special legal rights to inventors to enable them to profit from their ideas. This process began in an ad hoc fashion as isolated inventors were granted special "letters patent" from the sovereign; later on the process was rationalised with the establishment of government patent offices with equitable criteria.

It is only natural that a variety of perspectives have developed around this venerable institution. The legal practitioner views the patent system somewhat differently from the more abstract jurist, while the economist also has a unique point of view. Each approach has its own explanation as to what patents are, why we grant them, and how they are obtained. Each approach, when carefully examined, displays unique ethical insights as well.

The legal approach to patents

Patent legislation typically formulates a kind of contract between the sovereign and the inventor, in which the patent right is viewed as a reward for and thus a stimulus to innovation. Legislation and relevant treaties combine with the tradition of case law to create the patent regime in a particular jurisdiction.

A typical example is the United States Constitution, which gives the Congress the power to "promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries".[215]

From here we see that a patent is an "exclusive right", and it is granted for the instrumental goal "to promote the progress of science and useful arts".

Patent protection is not meant only to encourage the production of new inventions, it is also designed to encourage their disclosure. By giving protection which is broader than that granted to trade secrets, inventors are encouraged to publicise their innovations by publishing a patent. Keeping an

215 United States Constitution, section 7 paragraph 8.

invention secret stifles innovation by preventing others from using it or from learning from it, and wastes resources because keeping a secret can be very costly.

The exact criteria which are considered to successfully attain this goal have evolved through a centuries-long process of trial and error, and today patentability of an invention depends on the nature of the invention, its subject matter, and its intended use.

Nature of invention

In order to be patentable an innovation must have three qualities: it must be novel, useful, and non-obvious.

The novelty criterion is evaluated by verifying that no such invention is recorded in "prior art", that is the body of existing record of innovation.

Despite its name, the usefulness criterion is not meant to exclude inventions which are "useless", which do not need any protection. Rather, it is meant to withhold protection from innovations which are general or theoretical in character, and which do not clearly enunciate what specific use and practical benefit they are expected to produce.

The non-obviousness criterion is evaluated by asking if the average skilled person in the relevant field of knowledge could have been expected to conceive the same idea.

These criteria are directly related to the purpose of the statute. Giving protection to inventions which are not new or not innovative doesn't promote innovation, it stifles it. Such protection would take inventions which already exist or which could easily be conceived and remove them from the public domain, so that anyone who wanted to use them would have to secure the permission of the patent holder.

Likewise, giving protection to inventions which are not "useful" gives much more protection than is necessary, because a general idea will typically encompass a vast ambit of potential inventions. Furthermore, the inventor will have less incentive to perfect the invention because such refinements are not needed to obtain a patent.

Subject matter

Patents are granted on products and processes; many useful innovations are considered neither products nor processes and are not eligible for patents. For example, in the United States new plant varieties which are sexually reproduced are not patentable, but rather are protected by the Plant Variety Protection Act of 1970.

This limitation is very significant for the biotechnology industry, since the novel nature of biotechnology inventions repeatedly raises the question of whether they fall into the category of patent statutes which speak of "manufactures", "compositions of matter" and the like. Indeed, a recent Canadian Supreme Court decision ruled that the Harvard oncomouse, which is a mouse with

certain genetic anomalies bred in by a sophisticated process, is not patentable. The court did not deny that the oncomouse is novel, useful, and non-obvious; rather, the majority concluded that a higher life form such as a mouse is not a "composition of matter" according to the intent of the statute. Therefore, a process patent on the procedure for producing the mouse was allowed, but a patent on the mouse itself invalid. It is now up to the legislature in Canada to clarify this issue.[216]

The subject matter restriction has a salient ethical aspect. An invention which is not a "product or process" is considered to lack the required degree of artificiality which would justify giving a property right. The seemingly technical conclusion of the Canadian court concluding that mice are not "products" actually bases itself on many considerations which are clearly ethical in nature. For example, the majority opinion points out that a higher life form is "generally regarded as possessing qualities and characteristics that transcend the particular genetic material of which it is composed".[217]

The Canadian Supreme Court also considers that allowing such patents, while prohibiting patents on human beings, would require the court to pass judgment on where to draw the line – hardly a simple matter in the world of biotechnology where transgenic species are the rule rather than the exception! The court ruled, "It is not an appropriate judicial function of the courts to create an exception from patentability for human life given that such an exception requires one to consider both what is human and which aspects of human life should be excluded." This is not a function for the court but rather "presumably will require Parliament to engage in public debate, a balancing of competing social interests, and intricate legislative drafting."[218]

Intended use

Another important requirement is that the exploitation of the invention should not contradict public order or public morality. For example, the European Patent convention states that "European patents shall not be granted in respect of inventions the publication or exploitation of which would be contrary to 'ordre public' or morality".[219] Traditionally this stipulation was used to withhold protection from dangerous inventions such as weapons, but at least one country has broadened this concept to include patents on human organs, which are considered contrary to human dignity.[220]

This condition has an evident ethical basis. Since patents are meant to promote the "useful arts", there is an obvious public interest in promoting only those arts whose use is beneficial to humanity.

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216 Harvard College vs. Canada (Commissioner of Patents).2002 SCC 76 File no. 28155. Available from: URL: http://www.lexum.umontreal.ca/csc-scc/en/rec/html/harvard.en.html.

217 Ibid section B (1).

218 Ibid section B (2).

219 European Patent Convention part II chapter I article 53(b)ited 2003 May 8]. Available from: URL: http://www.european-patent-office.org/legal/epc/e/ar53.html. Accessed May 8, 2003.

220 Code de la proprieté intellectuelle. Legislative section, Book VI, chapter 1, article L 611-17. Available from: URL: http://www3.ccip.fr/irpi/code-propriete. Accessed May 8, 2003.

Natural law approach to patents

The law of intellectual property, like that of tangible property, is often conceived as resting not on the basis of legislative fiat but rather on basic moral principles. Most people feel that stealing objects constitutes a fundamental moral outrage which is not dependent on a precise statutory definition of property; this approach can be extended to stealing ideas.

In this approach the inventor's ownership of his or her idea is a natural outgrowth of the intimate personal connection the innovator has with the fruit of his or her unique creative capacity. This unique connection is formalised in a legal right of exclusivity. A report from the United States Office of Technology Assessment states that some arguments "justify property rights as entitlements to the fruits of one's labor and draw upon themes derived from John Locke's seminal discussion of property rights".[221]

This approach would give us a somewhat different understanding of the various criteria:

Nature of invention

An idea that is not novel is not the fruit of the inventor at all, but rather of someone else. And if the idea is not obvious, the connection with the inventor is rather tenuous: the invention is not the fruit of his or her unique creativity but rather of his or her professional training, which is shared with an entire community of similarly skilled individuals.

The usefulness criterion could be understood according to this approach by suggesting that natural-law ownership cannot extend to anything which is beyond the owner's ability to encompass and exploit. Locke states: "As much as any one can make use of to any advantage of life before it spoils, so much he may be labour fix a Property in. Whatever is beyond this, is more than his share, and belongs to others."[222] In a natural-law framework, a person can acquire a field but not a continent. Extending this idea to intellectual property, we would not be willing to acknowledge ownership over a law of nature with its vast potential for new products and processes.[223]

Subject matter

The restrictions on subject matter have a particularly intuitive interpretation according to a natural law approach. Certain physical entities have such a

221221 U.S. Congress, Office of Technology Assessment. New Developments in Biotechnology: Patenting Life – Special Report, OTA-BA-370. Washington DC: US Government Printing Office, April 1989. p. 130. Available from: URL: http://www.wws.princeton.edu/cgi-bin/byteserv.prl/~ota/disk1/1989/8924/892410.PDF. Accessed May 8, 2003.

222 Locke John. Second Treatise on Government. Swansea: University of Wales Swansea. Chapter 5 paragraph 30. Available from: URL: http://www.swan.ac.uk/poli/texts/locke/lockcont.htm. Accessed May 22, 2003.

223 This approach to intellectual property has use in explaining patents, but is particularly valuable in understanding copyrights. Copyrights are granted even when the artistic works have little economic value and even when the investment required to produce them is small; they also last for a much longer time than patents. The creative input in producing a work of art is greater than that in producing an industrial invention, so the greater applicability of the natural law approach is understandable.

salient public character that no one would think of providing property rights in them, and the same applies to intellectual entities.

For example, it is hard to imagine that the citizens of the United States would ever consent to granting private ownership of the Statue of Liberty, even if there were iron-clad assurances that access and upkeep were safeguarded and even improved. The Statue is such a most prominent symbol of American freedom and international friendship that the very fact of private ownership would demean its importance.

By the same token, certain ideas have a salient public character which in itself has immense public worth. One example might be the earth's biological inheritance. The general consciousness that this inheritance belongs to all mankind might be of greater value than any economic benefit that would be obtained by allowing private ownership of plant varieties which are obtainable by ordinary cross-breeding.

Economic approach to patents

The economist has no difficulty identifying a patent as an instance of legal monopoly. The economic justification of this monopoly has its roots in the fact that ideas are a "public good": one individual can use them without depriving another, and furthermore it is technically impossible for one individual to exclude others from using the good.

Ideas are free to use, but they are expensive to produce. And since ideas are a public good, the innovator of the idea is unable to recoup his investment in producing them. After the inventor pours a thousand, a million, or a billion dollars into his idea, others can benefit from them without any payment. In order to maintain an incentive to create and disclose innovative ideas, some kind of reward is necessary; and for a variety of reasons giving a legal monopoly has been considered one of the most effective types of reward.

In a seminal economic analysis of patents, William Nordhaus wrote that "information is expensive to produce, cheap to reproduce, and difficult to profit from". One solution is patents, which are "licenses for a monopoly on information for a specified period of time".[224]

According to this point of view, the three patentability criteria are meant to maintain an appropriate balance between the extent of the investment and the extent of the reward. We don't want to make the reward to innovation so small that inventors will not find it worth their while, yet we also don't want to make the reward so large that the social cost is excessive. As Nordhaus remarks in regard to patent lifetime, "First, a longer life increases invention . This is a positive effect. Second, a longer life means that the monopoly on information lasts longer and thus there are more losses from inefficiencies associated with monopoly."[225]

224 Nordhaus William D., Invention, Growth and Welfare: A Theoretical Treatment of Technological Change. Cambridge MA: MIT Press; 1969. p. 70.

225 Nordhaus p. 76.

It follows that novelty and non-obviousness are requirements because pre-existing or obvious inventions can be produced at little cost. Therefore, it is unjustified to offer a large reward for coming up with them. Richard Posner writes, "The functional meaning of obviousness is discoverable at low cost. The lower the cost of discovery, the less necessary patent protection is to induce the discovery to be made."[226]

Conversely, usefulness is required for patentability because a patent on an invention that is too general will have immense economic value. Even if the idea does require a large investment, granting a patent will give a reward incommensurate with the effort required to produce the idea.

3 HOW SCR PATENTS CAN BEST STIMULATE PRODUCTIVE RESEARCH

Patents are designed to encourage productive investment in beneficial ideas, but no guarantee exists that they will achieve this aim. A patent system which is poorly designed can overly restrict access to inventions; can induce too little investment or too much; and can also encourage undesirable activities. All of these concerns have been raised with regard to biomedical research; one influential paper summarises this view by stating that "Commercial incentives are widely assumed to contribute to human health, but this is not necessarily the case. There is growing concern that market principles have been improperly applied."[227]

The problem with patents

Once a product has already been invented, patents are problematic because they are monopolies, implying the problems of increased price and reduced availability. Since monopolists are shielded from competition they have less incentive to offer competitive prices. This loss is supposed to be the trade-off necessary to induce invention in the first place. However, while the patent system does work well on the whole there is no guarantee that in any particular area of concern it will succeed in encouraging research and development.

Following is a partial list of ways in which a patent regime may fail to induce the appropriate, economically-efficient benefit from research and development:

If patent protection is inadequate, there will be inadequate incentives to create and publicise new inventions. Inventors will find that new ideas are not worth the investment because others will steal them, or they will make new inventions but keep them secret.

Conversely, the monopoly power of a patent holder may, ironically, provide less incentive to further innovation. Innovation is one way of obtaining a

226 Posner Richard A. Economic Analysis of Law. 4th edition. Boston: Little Brown and Co.; 1992. p. 39.

227 Nelkin Dorothy, Andrews Lori Andrews. Homo Economicus: Commercialization of Body Tissue in the Age of Biotechnology. Hastings Center Report 1998 Sep-Oct: 30-39. p. 37.

competitive advantage; if the monopoly rights are too extensive the patent holder may be able to "rest on his laurels" and refrain from further innovation.

If patent protection is too extensive, then too much may be invested in innovation. Wasteful patent races may develop where a number of firms invest large sums in substantially identical research, each one hoping to be the first to obtain a patent and enjoy excessive monopoly revenues.

When the scope of patent protection is not clearly defined, the result may be very expensive litigation.[228] A related cost is that of "defensive patenting" where patents are not needed to protect innovations from competition but are taken out to defend against infringement suits and conversely to threaten competitors with these suits.[229]

When commercial application of a patent requires combining ideas from a number of patent holders, negotiations among the various rights holders may be so complicated as to preclude effective exploitation of the various rights. This effect has been called the "anticommons" in an influential article.[230]

Sometimes the research necessary for innovation may itself be socially undesirable. For example, some research has involved denying treatment to patients or engaging in intrusive or dangerous treatments that would not be indicated on therapeutic grounds. While this is not exactly a failure of the patent regime, it can be one result of the incentives created by such a regime.

We will devote a short section to the ways in which the economic theory of patent answers these concerns in general and, where appropriate, to specific concerns relating to SCR. A more detailed discussion is beyond the scope of this paper, belonging more properly to a survey of patent law in general.

How do SCR patents measure up?

Let us examine the consequences for patent policy of each of these considerations in the context of SCR. The main source of information in the analysis of the stem-cell research business is the biweekly newsletter Stem Cell Business News.[231]

MONOPOLY PROFITS: Various schemes exist which spur innovation yet avoid the problem of monopoly profits. Two examples are direct government sponsorship of innovation or awarding a money prise to an inventor. (Mandatory licensing is one version of this.) Research suggests that these alternatives are generally inferior solutions for patentable innovations, because only the innovator has a clear idea of the value of the invention. The government has much less knowledge and is unable to adequately assess the

228 Of course this litigation is not completely without social benefit. Some litigation is necessary precisely to help clarify the exact extent of patent protection on the basis of judicial precedent. But careful attention at the stage of legislation or of patent writing can often provide the same degree of clarity at far less expense.

229 Hall Bronwyn, Ziedonis Rosemarie Ham. The patent paradox revisited. RAND Journal of Economics 2001 Spring; 32 (1):101-128.

230 Heller Michael A, Eisenberg Rebecca S. Can Patents Deter Innovation? The Anticommons in Biomedical Research. Science 1998 May 1; 280: 698-701.

231 Stem Cell Business News. Leesburg, VA: DataTrends publications.

true value. Thus they are likely to provide inadequate compensation for some ideas while spending excessively on others. Monopoly rights ensure that the inventor recoups an amount, which is roughly proportional to the social value of the invention.

Complacency

The patent system strives to avoid this problem mainly through limitations on a patent's scope. Such limitations are meant to ensure that a patent provides adequate incentive to innovate but doesn't excessively deter other inventions. A patent, which is of appropriate breadth, can be invented around at an expense which is significant but not prohibitive. In this way, the competitor has an incentive to take out a license rather than engage in wasteful duplicative invention, but the patent holder has an incentive to offer a license at a reasonable price knowing that an excessive demand will make it worthwhile for the competitor to invent around the patent.

Complacency does not seem to be a feature of the stem cell research industry, which is characterised by dozens of relatively small companies, none of which has a dominant position in any broad technology, and all of whom are fiercely competing for financing and market share.[232]

Inadequate protection

Inadequate patent protection is a deterrent to investment if inventions cannot be kept secret. There is no evidence that inadequate protection is an obstacle in SCR. While 2002 was a very hard year for the industry, none of the various analyses we found in the press attributed this problem to inadequate IP protection, and companies freely entered into many licensing agreements indicating that they feel their proprietary techniques and cell lines are adequately protected. One publication claimed that in Canada, "99% of companies rely on patents (rather than products) as their sole source of value".[233] Another, exhaustively researched paper concludes that "virtually all biotechnology discoveries are patented".[234]

Patent races

Stem cell research is advancing on so many different fronts there does not seem to be any single "mega-invention" out there which companies are working on simultaneously. The business seems to be characterised by a huge number of niche technologies, which enable each of the large number of small firms to develop its own particular IP portfolio.

232 In an examination of about nine months of the newsletter during 2002 and 2003, dozens of companies were significant enough to be considered newsworthy. No company dominated the news.

233 Patenting pieces of people. Nature Biotechnology 2003 April; 21(4):341.

234 Lerner Josh. Patenting in the shadow of competitors. Journal of Law and Economics 1995 Oct; 38:463-495. p. 464.

Uncertain scope

nother way in which patents can deter innovation is if they are of uncertain scope. Such uncertainty invites expensive and wasteful litigation. Sometimes patents are taken out with the sole intent of bullying competitors in court.[235] The remedy is to strive to have transparent rules establishing when a patent is infringed.

Practically speaking, the stem cell business seems to be characterised by little litigation – perhaps due to the staking out of niches as previously described. Over a period of over nine months, the Stem Cell Business newsletter reported on dozens of companies whose success depends on proprietary products and on nearly the same number of IPR transfers through licenses, sales, acquisitions or MTA's, but only a handful reported patent disputes!

Anticommons

A prominent recent paper suggests that special problems may arise from patents on "upstream" technologies. If many different "upstream" inventions are required to produce any particular "downstream" application, then negotiations may be prohibitively difficult.[236]

However, experience shows that the profit motive provides significant motivation for these upstream patent holders to find ways to overcome obstacles to negotiation. In the case of SCR, we see a pattern of patent holders trying at first to maintain very restrictive arrangements with licensees, but after a year or two conceding that a more accommodative policy is necessary. This suggests that the anticommons problem is real but temporary.

For example, a number of firms made high-profile licensing agreements in the summer of 2001. The Scientist cited Q. Todd Dickinson, a former commissioner of the U.S. Patent and Trademark office, as saying "In reality, all these licensing issues are fairly straightforward. I don't think there's anything here that's unusual, aside from the visibility and the fact that it's gotten to the presidential level as a matter of public policy. I've seen much more complex licensing schemes than this. It can look kind of complex, but this is pretty simple stuff. It's a pretty garden-variety kind of licensing program."[237]

In addition, the structure of the SC research business seems to be rather flat – more like a geyser field than a stream. Many companies have parallel but slightly varying versions of basic technology, with no single technology critical to a large swathe of research. So the basic presumption of the anticommons model, a situation where many technologies are needed for a useful product, does not seem to be applicable in this market. When licensing agreements are called for, there do not appear to be daunting obstacles to arranging them.

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235 This phenomenon is documented in Hall and Zeidonis, above. Their research suggests that this problem may be particularly troublesome in technologies with a short product lifetime and with relative ease of keeping trade secrets. These traits do not seem to characterize stem cell research, which so far has displayed very long product cycles and in which trade secrets are relatively unimportant as a means of protecting intellectual property.

236 Heller and Eisenberg.

237 Agres Ted. Stem cells: steady momentum towards funding. The Scientist 2001 Sep 17; 15[18]:8. Available from: URL: http://www.the-scientist.com/yr2001/sep/agres_p8_010917.html. Accessed May 22, 2003.

Undesirable research protocols

Even when the innovations encouraged by patent law are desirable, the research that leads to these innovations may have undesirable elements. Sometimes research activities are inherently unethical, as when vital medical treatment is withheld or when experimentation is damaging to subjects. In other cases, the profit motive may create conflicts of interest, which will create an incentive for unethical activities.

These collateral effects of a patent system will be discussed in the next section of the paper.

Summary – effects of patents on research

From an economic point of view, there doesn't seem to be anything special about SCR, which would recommend a unique, sui generis intellectual property regime. On the contrary, the current patent regime seems to be working remarkably well.

A survey of the business literature reveals that there are a large number of small companies each developing a specific niche of the market for SC research applications, where the value of each company is largely dependent on its proprietary knowledge or biological materials. A large fraction of companies' revenue is reported to be derived from sales or licensing agreements or material transfer agreements. In addition, there are a large number of acquisitions in which IP portfolios are listed as a significant consideration in the target firm's value. We cited above an industry report claiming that for virtually all firms, revenue is derived exclusively from patents. Over a period of almost a year, only a handful of patent infringement disputes were mentioned.

One prominent researcher did mention that material transfer agreements were an important obstacle in obtaining high-quality cells.[238] However, patents were not mentioned. Furthermore, joint testimony of the United States stem cell industry before a Senate panel decried the many obstacles in obtaining cells, but IP considerations were not mentioned at all.[239]

Various explanations for the poor performance of biotech stocks over the year 2002 tended to focus on the poor performance of the market as a whole, loss of investor confidence to a prominent scandal, and concerns over possible political obstacles to continued research. No analysis mentioned legal IP problems such as inadequate protection, blocking patents, or dissipation of resources in infringement battles.

The lack of problems due to IP difficulties in the past does not mean that such problems can not arise in the future. Experience suggests that in rapidly developing technologies there can be a danger that the same type of innovation, which is non-obvious at one stage, may become routine and hence

238 Dalton Alastair. US firms blocking stem cell research. The Scotsman 2002 Oct 17. Accessed from: news.scotsman.com, October 24 2002.

239 Stem cell researchers voice their frustration over Bush policy. Stem Cell Business News 2002 Oct 4;1(11). p.1.

non-patentable at a more advanced stage of development. Therefore, the following guidelines will be appropriate:

Patents should be given only for innovations, which are truly new and non-obvious, not for the accreted discoveries, which are a routine part of laboratory research. This distinction is a dynamic one, and the same type of innovation, which is new today, may become routine in a few years' time.

Patents should be given only for innovations, which have a concrete promise of useful application, not those for which any potential use is only speculative.

Examiners and courts should ensure that the exact boundaries of patent protection are as clear as possible. Such a "bright line" will help eliminate costly court battles. These battles are a setback to research in themselves, and their prospect can deter inventors from entering the fray in the first place.

4 IMPACT OF IP REGIME ON ETHICAL PROBLEMS IN STEM CELL RESEARCH

4.1. Introduction

In the previous section, we asked how a patent system can be designed to induce enough effective research; in this section we discuss how it can avoid creating destructive research practices. In this way we address the ethical problems of commission and not only those of omission.

One troubling ethical problem of embryonic SCR is the practice of destroying in vitro embryos to extract stem cells. This issue is beyond the scope of the IP section of this paper, because this question is equally present no matter what IP regimen is guiding the research. Whatever IP system is adopted will be required to take steps to discourage any research which is improper from the point of view of bioethics. If there are no specific laws against a specific practice, then the IP system can be used as a tool; for example, some practices may be considered as unpatentable due to a conflict with public order and morals; or if the main source of innovation is government funding this funding can be withheld from problematic types of research. However, this evaluation has no area of overlap with the study of IP regimens per se.

Another possible difficulty is that the economic advantages of SCR patents may create new conflicts of interest between patients and treatment providers. The ability of the physician to obtain lucrative property rights based on biological material from patients creates an incentive to extract these materials with inadequate consent or lacking consent altogether. This problem exists with respect to all types of (stem) cells: individuals who are donating their own cells (adult stem cells); new mothers donating placental or umbilical cords; abortion patients donating the aborted fetus; IVF clients donating unused embryos; or women donating their eggs for SCR.

This problem can take many forms. A pure "donor" relationship may be influenced by duress, as when a fertility clinic exerts subtle pressure on clients to donate unused embryos as a tacit condition for continued treatment, or when the economic incentives for egg donation are so great as to impair the judgment of indigent young women.[240]

When required medical procedures yield economically valuable biological materials, the patient may be inadequately informed of the value of these materials so his or her waiver of rights to these materials may lack full informed consent from an economic point of view.

The choice of medical procedure may be consciously or unconsciously biased by the desire to obtain such biological material. The patient's consent to the procedure itself may not be fully informed if the treatment provider gives a skewed explanation for the desirability of a particular course of treatment or diagnostics.

We can identify a variety of ethical questions related to this aspect of medical research:

- Is the allocation of profit between physician and patient equitable?
- Is there true informed consent on the part of the patient?
- Does the research regimen prevent the patient from obtaining adequate care?

Such care could be withheld either because the treatment provider has an incentive to deprive the patient or because the lack of trust between patient and physician keeps the former from undergoing tests and procedures, which are truly necessary.

Informed consent

At least since Kant enunciated his "practical imperative", ethicists have acknowledged the importance of treating others as ends in themselves by respecting their autonomy, and not only as a means to an end. This autonomy can be violated by outright coercion or by more subtle forms of guile.

Since patients are a means for medical researchers to obtain valuable scientific knowledge, such researchers have to take particular care to respect the wishes of patients and research subjects by obtaining adequate consent. While national legislation as well as international agreements such as the Helsinki Declaration provides guidelines for informed consent, experience teaches that declarations are not enough and there is also a need to structure the treatment environment in a way that does not encourage bypassing true informed consent.

240 Healy Bernadine. Donors at risk: the high cost of eggs. US News and World Report [online newspaper] 2003 Jan 13; Health section. Available from www.usnews.com/usnews/issue/030113/health/13donor.b.htm.Accessed January 7, 2003. A similar phenomenon is documented in a BBC report claiming that residents of Moldovia have donated kidneys for as little as $3,000 because of financial distress. Bell Bethany. Moldovia's desperate organ donors. BBC News 2003 May 21. Available from: URL: http://news.bbc.co.uk/1/hi/world/europe/3046217.stm. Accessed May 22, 2003.

These concerns are magnified when the medical knowledge obtained from research serves not only as a means to obtaining knowledge and recognition, but also as a direct means of enrichment. The ethical complication introduced by the profit motive is both quantitative and qualitative:

Quantitatively, the profit motive provides one additional incentive to obtain medically valuable biological material. But the profit motive is also qualitatively different from the other motives. The main difficulty is that this motive is not in itself ethically grounded. We will now elaborate on these two elements.

The profit motive as an obstacle to informed consent

The desire to obtain knowledge can be part of a selfish, acquisitive urge, as it was in the case of Dr. Faustus. But more often this desire is itself part of a desire to benefit humanity. To a lesser extent, the same is true of fame: a person seeks fame, not notoriety; he or she wants to be acknowledged as someone who did something extraordinary to benefit others.

Since these inducements to medical research are themselves ethically grounded, the concern for patients' rights is likely to be an effective, if partial, counterbalance. This concern will constitute part of the encompassing ethical calculus.

However, the desire for monetary gain has a much less salient ethical aspect. While we do observe that people desire to obtain wealth in order to spend it on socially worthwhile ends, such ethical motivations are usually a much smaller part of this kind of acquisitiveness. The result is that the "ethical counterbalance" of patients' rights will have less impact. Indeed, this consideration can even outweigh the desire for knowledge and fame and lead individuals to engage in research which is lucrative yet not particularly informative.

The conclusion seems to be that from a psychic point of view, a profit system carries a greater risk that the practitioner will fail to view ethically correct treatment of the patient as an integral part of his medical practice. We can identify a number of ways of dealing with the problem created by the profit motive:

One way is just to eliminate the profit motive altogether. In our case, if we were to disallow patents on stem cell research then the practitioner would not stand to make substantial sums from any innovations based on biological material from patients. This alternative can be attractive if other motives are sufficient to induce intensive research.

We could rely on the market itself to remedy the problem. Perhaps we could rely on competition to incentivise practitioners to act in an ethical way, thus enhancing their reputations and their clientele.

We could promulgate regulations which create economic incentives to informed consent. For example, an "eminent domain" approach can solve some of the negative incentive problems, as we explain below.

Finally, we could seek to structure research protocols in a way that encourages ethical rather than market approaches to decision making. The idea is not to create economic incentives to obtain informed consent but rather to induce the researcher to apply ethical criteria to this issue, instead of economic criteria.

Let us analyse each of these directions.

Eliminating the profit motive

While the profit motive is undoubtedly one powerful way of unlocking human energy and creativity, it is not the only way. It is worth examining whether other motivations such as love of knowledge and the desire for recognition and academic advancement might not be equally effective without creating the same problems of informed consent.

It is true that the dash to recognition, no less than the dash to profit, may trample patients' rights. Indeed, some of the worst examples of ethically repugnant treatment of research subjects were in government-sponsored studies.[241]

However, there are two reasons to believe that in general public sponsorship could achieve better treatment of patients. One is the culture of public service which we expect from the public sector; this is related to the point we made above that the entire organizational orientation is basically an ethical one. The other factor is the openness and transparency, which characterises the public sector and the academic environment, as compared with the culture of secrecy, which is such an essential part of competitive industry.

Working against this consideration is the fact that competition is a critical and highly effective stimulus to positive treatment of clients. When the public sector tramples the rights of subjects they may have no alternative but to suffer.

It seems that public-sector research should be viewed as an essential adjunct to the private sector. In this way public sector involvement increases competition rather than decreasing it. Government-financed studies will bring a public-service mentality and public-service transparency, yet will both face and provide competition for ethical behaviour vis a vis the private sector.

Creating market incentives for informed consent

When faced with a patient whose tissues may have monetary value, a treatment provider might want to withhold this knowledge from the patient for one of three economic reasons:

241 One notorious example is the Tuskegee syphilis study in the United States, where researches deprived syphilis sufferers of treatment for decades in order to study the course of their disease. In the meantime the patients' health deteriorated and they continued to infect others with this dangerous disorder. No one got rich or famous from this study, and even the scientific value of the results is not particularly impressive. It seems that bureaucraticsm can be at least as heartless as avarice.

The physician might want to appropriate this monetary value for himself and not share it with the patient;

The physician might fear that revealing the value to the patient would lead to an intractable bargaining situation.

The physician might feel that even if offered an appropriate monetary inducement the patient would withhold consent.

In economic terms, the first scenario presents an "equity" problem, the second and third an "efficiency" problem: The first scenario assumes that the social value of the biopsy will be realised; the question is who will appropriate it. In the second case, seeking informed consent may introduce a market failure (bilateral monopoly), which leads to a socially desirable test not being performed. In the third scenario, not seeking informed consent introduces a market failure, which leads to a socially undesirable test being performed: the patient endures excessive discomfort, which is not justified by the economic value of the test.[242]

242 These concepts can be clarified through a simplified abstract example. This is an economic, cost-benefit model in which we will assume that all benefits and costs can be quantified. While in an actual situation we will want to know the relative weight of economic incentives as against medical or ethical considerations, the purpose of this model is to isolate and examine the specifically economic dimension of this problem.

Let us suppose a certain biopsy is likely to have some economic value due to its use in medical research. In addition, the biopsy will make a certain contribution to the patient's own well-being. On the cost side, the patient evaluates the discomfort of the biopsy as "costing" him a certain sum. (In addition, the biopsy may have some economic cost to perform; we will ignore this consideration since it is not relevant to the phenomenon we are trying to understand.)

To be precise, suppose that the research value of the tissue is one thousand dollars, the medical contribution of the test to the patient is also one thousand dollars, and the discomfort of the test is also one thousand dollars. Then the social value of the test is one thousand dollars, and the economically efficient outcome is that the patient accepts an inducement of between zero and one thousand dollars to consent to the test and grant economic rights to the treatment provider. From an equity point of view, the "fair" division of the economic surplus is dependent on a variety of considerations, but elementary fairness suggests that half and half is equitable: the patient gets a $500 royalty and the treatment provider will earn the same sum from use or sale of the tissue sample.

In the context of this example, we might depart from this ideal for any one of the three reasons mentioned above. These considerations would be expressed as follows:

In the first case, the physician believes that the informed patient would accept a five hundred dollar inducement to carry out the procedure, but prefers to keep this sum for himself.

In the second case, the physician is worried that even though the fair allocation is to split equally the thousand dollars added value, the patient will demand the full thousand dollars or even more, an excessive amount, and the result will be that no test will be performed and no one will benefit.

In the third case, the physician is worried that the patient is so afraid of the biopsy that even one thousand dollars would not induce agreement.

In each of these cases, the treatment provider has an economic incentive to violate professional ethics and exaggerate the true medical necessity of the test, convincing the patient that even without an inducement it is in his interest to have the test done. Alternatively, the physician may fairly state the medical value of the test, allowing the patient to consider that the test is worthwhile since the medical value to him is equal to the discomfort. Yet the physician may withhold knowledge of the research value so as not to be faced with a demand for an inducement.

While the issue of informed consent is framed in terms of a physician ordering "unnecessary" diagnostic tests, we see from these examples that tests may be unnecessary from an individual point of view but necessary from a social point of view. In the first two scenarios the tests should be done; only in the third is the procedure truly superfluous.

The second case should be particularly worrisome, because it demonstrates that from a cost-benefit perspective, the demand for informed consent can actually be counterproductive. The sense of unfairness is greatest in those high-profile cases where the physician makes a fortune from the patient's suffering, yet it is exactly in these cases where informed consent may be an obstacle to equity!

Let us take the well-known case of John Moore, whose treatment providers made millions of dollars off a patent based on his biological materials, which were taken from him without false pretences. There can be little doubt that if they had offered Moore a share of this money that he would have consented to the additional tests, which were intrusive but not in any way dangerous.

Yet full disclosure could well have resulted in a disastrous market failure. Had Moore known of the value of his tissues, we would have a situation of "bilateral monopoly" which could easily have ended in stalemate. The patient would have had a monetary incentive to threaten to hold out for a large sum, which might not have been forthcoming. This would have resulted in the loss of millions of dollars of social value, as measured by the market value of the patents.

In many cases, law resolves problems of bilateral monopoly by establishing a fixed statutory standard of recompense. For example, in the case of salvage of a ship in distress the salvor is entitled only to reasonable recompense. This keeps the salvor from demanding an exorbitant price, which could lead to an inequitable outcome or even to a breakdown in negotiations. If the amount is insufficient, the salvor can decline.[243] Another example is unjust enrichment, where a person who performs a service is entitled to fair recompense although no negotiations took place.[244]

The parallel in our case is to establish an equitable statutory recompense for biological materials, and presenting both patient and physician with a take-it-or-leave-it choice.[245] The physician will not benefit from hiding his material benefit, because the "unjust enrichment" aspect of the payment will compel him to pay even without negotiation. He will not need to fear patient holdout, because the patient is faced with a take-it-or-leave-it offer. And if the patient truly believes that the compensation is inadequate for his troubles, he can always refuse to take part.

Of course in an actual treatment setting there would be many additional considerations, including the difficulty of quantifying medical value and patient discomfort and the existence of ethical norms and rules. However, it is important to understand the cost-benefit dimension of the issue in isolation

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243 See for example Posner, p. 116-117.

244 See Posner p. 133-134.

245 In the above example, we might establish a statutory recompense of five hundred dollars for this particular test as long as the physician makes at least this amount.

In the first case, the physician has no incentive to mislead the patient, because even without patient consent recompense is mandatory.

In the second case, the patient has no incentive to hold out for a larger sum because the law requires him to accept five hundred dollars or nothing.

In the third case, the patient will refuse to undergo the procedure because the recompense is insufficient, and this is the efficient outcome.

before we combine this perspective with other considerations. A fixed payment schedule established by regulatory policy could encourage informed consent in tissue donations.

Encouraging ethical decision making

The careful cost-benefit analysis we just performed suffers from a significant ethical lacuna: it assumes that costs and benefits can be calculated independently of their ethical context. The approach presented above assumes there are quantitative measures of how much the biopsy hurts and how much the research is worth to patients.

Yet introspection and research both confirm that the "utility" of acts is intimately dependent on their meaning. The same procedure, which may be considered unbearably painful in one context, may be cheerfully borne in another.

This claim was forcefully made by Richard Titmuss in his highly influential book on donating blood, a topic which can serve as a paradigm for other types of tissue donation. After an exhaustive examination of blood donation procedures in a number of countries, Titmuss concludes: "The evidence in preceding chapters shows the extent to which commercialization and profit in blood has been driving out the voluntary donor. Once man begins to say, as he sees that dollars exchange for blood supplies from Skid Row and a poor and often coloured population of sellers 'I need not longer experience (or suffer from) a sense of responsibility (or sin) in not giving to my neighbour' then the consequences are likely to be socially pervasive."[246]

Utilitarian analysis would encourage us to compare the value of blood to the inconvenience and discomfort of donation, and settle on an appropriate recompense. However, Titmuss concluded that while donating blood is considered bothersome and painful when done for profit, it is considered inspiring and uplifting when done as an act of altruism. His study was highly influential in leading to a change in donation policy in the United States that almost completely eliminated paid donations.

The general applicability of Titmuss's conclusion is still a subject of controversy. One subsequent study opined, "One difficulty of Titmuss's argument is that he never proves it."[247] It is still possible that on the whole the extent of donations would be greater under a system of paid donors. However, the presence of such an attitude to some extent is certainly borne out by Titmuss's interviews. As he writes, "Practically all the voluntary donors whose answers we set down in their own words employed a moral vocabulary to explain their reasons for giving blood."[248]

246 Titmuss Richard M. The Gift Relationship - from human blood to social policy. New York: Vintage Books, Random House; 1972. p. 198-199.

247 Hough Douglas. The Market for Human Blood. Lexington MA: Lexington Books; 1978. p. 29.

248 Titmuss p. 237.

This in turn suggests that the market solution suggested in the previous section is actually quite deficient. While the statutory payment regimen is the ideal solution given the costs and benefits, it will not be optimal if the costs are themselves endogenous to the regimen. In other words, the very fact that this solution is enunciated in market terms vitiates the ethical motivation for donation and thus deprives the patient of an important source of satisfaction from his or her contribution to medical advancement.

Let us examine a variety of possible solutions:

Inducement limited only at locus of donation

One obvious solution would be to eliminate all kinds of inducements for tissue donation. This would be parallel to the existing situation in blood donation, where the blood banks obtain blood free from donors and afterwards sell it as an ordinary commodity to hospitals or other blood banks. A problem with this approach is that it may violate equity.

In the case of James Moore, his physicians obtained a commercially valuable patent on a cell line derived from his excised spleen, though the consent he gave was limited to non-commercial research use. When Moore sued the physicians for conversion (improper use of his property), the defendants maintained that these cells were not property at all. The Court of Appeal pointed out the paradox in this position, stating: "Defendants' position that plaintiff cannot own his tissue, but that they can, is fraught with irony."[249]

Payment to a third party

One way of dealing with the equity problem would be to provide for payment to some third party. For example, some fraction of the commercial value of donated tissue could be donated to some kind of fund, which would help patients. We could imagine that some proceeds from blood sales by blood banks would help finance transfusions for needy recipients, and so on.

In this way the economic value of the donation is realised in an equitable way without granting a salient commercial character to the act of donation.

Non-demanding form of payment

A desirable goal would be to provide some kind of monetary payment to provide a sense of equity yet still maintain the mentality that the main reason for the donation is to help others. Attaining this ideal requires careful thought.

While it is true that monetary payment generally goes together with market approaches to valuation, the exchange of money does not automatically erase the deeper aspects of human interaction. As we will demonstrate in more detail

249 Moore v. Regents of the University of California, 793 P.2d 479 (Cal. 1990). Available from: URL: http://www.richmond.edu/~wolf/moore.htm. Accessed May 22, 2003.

in section IV, money payment can be consistent with ethical motivation if the payment is not excessive, not the object of bargaining, and if it is appropriately designated.

In light of this insight, we might want to try and preserve the desirable economic incentives of the fixed payment scheme while still trying to emphasise the inherent human element of donation. Following are some possible suggestions how this could be achieved:

The payment should not be designated as "payment for valuable tissue" but rather as "recompense for trouble";

Ideally, the payment should not be an actual transfer but rather a credit. The work of Kahneman and Twersky and others shows that there is a significant difference in the way individuals view gains versus foregone losses.[250] (Of course this may not be practicable in countries where there is little or no deductible on medical insurance, whether private or public.)

An excessive amount of payment could actually be counterproductive, by having the effect of stamping the donation process as a market exchange and eliminating the altruistic motive.

Conclusion

Medical research runs a constant danger of violating the rights of research subjects by viewing them as merely means to obtaining medical knowledge, and this danger is augmented by the presence of a profit motive. These rights need to be safeguarded by obtaining informed consent for all procedures.

Yet physicians may be reluctant to solicit full and adequate informed consent, particularly with respect to the economic and financial aspects, either because of a desire to obtain personal benefit or out of a fear that excessive disclosure could result in frustrating and fruitless negotiations.

One solution to this problem is to impose a mandatory payment schedule for tissue donations that are used for commercial purposes. Obtaining informed consent does not cost the treatment provider anything, because even without it he would have to make a payment and even with it the patient is not given excessive leverage.

However, it is important that this payment not be perceived as defining the donation as a commercial transaction. Such a perception could have the effect of neutralizing the altruistic motivation for tissue donation. The desire to help others is a powerful and inspiring motivator, which is not less effective than the profit motive.

However, there still may be valid reasons to require some kind of payment, either to reinforce the altruistic motive or to maintain equity. In this case, it is important that the altruistic dimension of the donation be maintained. Any payment should be reasonable in extent and carefully denoted. Another

250 See for example Kahneman D, Tversky A. Prospect Theory: An Analysis of Decision under Risk. Econometrica 1979; 47:263-91.

desideratum would be to provide it as a credit and not as a cash payment, or to pay it to a charitable fund and not to the donor.

5 INTRINSIC OBJECTIONS TO PROPERTY RIGHTS IN STEM CELL RESEARCH

5.1. Introduction

There are two distinct dimensions to the ethical impediments that apply to granting property rights in living organisms: utilitarian and intrinsic. Granting patents may lead to undesirable conse-quences, or it may be ethically objectionable in and of itself.

In the previous sections we discussed the utilitarian considerations, which stem from the fact that granting property rights creates a particular set of behavioural incentives. We have to consider if these incentives are motivating people to act in an ethical way, which benefits society.

However, this debate also has an intrinsic dimension: perhaps it is inherently unethical, even absurd, to speak of granting intellectual property rights in living organisms. The very name "creatures" suggests that these beings are the products of the Creator; there is an obvious element of hubris in calling ourselves their "inventors". Furthermore, we are used to relating to living creatures, our figurative cousins, with a certain degree of empathy; the question arises if the reductionist attitude encouraged by a one-dimensional property relation may not constitute a tragic impoverishment of our spiritual world and our relationship with our environment.

This intrinsic impediment is obviously augmented when the living organism under discussion is man himself. Our most prominent value systems place man at the centre of our ethical world. The Biblical perspective views man as created not only by, but actually in the very image of the Almighty. The profoundly influential perspective of Kantian ethics views man alone as worthy of intrinsic ethical consideration, due to our unique level of rationality.[251] Arrogating to ourselves ownership of an aspect of mankind involves a far more serious aspect of hubris than appropriation of another aspect of creation. Likewise, the reduction of man to a mere object of trade is obviously more serious than the parallel reduction as regards animals or inanimate goods.

The commodification controversy

One term, which repeatedly arises in the debate over intellectual property rights in bioethics, is "commodification". The concern is that a cognitive relationship between man and some object that was formerly deep and nuanced becomes reduced to a merely utilitarian relationship which is shallow and barren.

251 Schneewind, J.B. editor. Lectures on Ethics. In: Heath Peter, Schneewind J.B., editors. The Cambridge edition of the Works of Immanuel Kant. New York: Cambridge University Press; 1997. 27:460.

Commodification is one way of relating to someone as a means rather than as an independent end. In particular, a commodity is viewed as a means to making profit.

The commodification of human beings would constitute an obvious violation of Kant's "practical imperative", his second formulation of the categorical imperative, which forbids treating other rational beings as mere means to an end.[252] From a Kantian point of view, it is not necessary that any degrading use be made of an individual for an ethical violation to take place; the problem is the point of view of the user. For example, if an adoption broker views the infant as a commodity only, then the relationship to the child has a dimension of exploitation even if both the natural and adoptive parents are concerned primarily with the child's well-being. Kant himself stated that sale of human organs for purely commercial purposes violates the categorical imperative.[253]

Philosophers since Kant have identified ethical problems with commodification of non-human property as well. Carlyle and Marx retained Kant's humanistic focus but pointed out that excessive commodification of objects can impoverish the human element otherwise present in exchange;[254] while Heschel goes farther and states that our relationship to our entire environment should be one of appreciation, and not merely manipulation.[255]

In the case of stem cells, the danger of commodification presents itself on all of these levels. Instrumental use is made of the nascent human being, of human tissue, and of human research subjects; the specifically human element of the patient-practitioner relationship is de-emphasised in favour of the commercial element; and natural phenomena are declared human property in an avowed attempt to facilitate their manipulation.

Of course the presence of danger often dictates merely caution, rather than avoidance. The spectre of commodification does not necessarily invalidate the use of intellectual property in stem cell research; it may merely obligate us to seek ways to minimise the hazards.

In order to study the problem of commodification in patenting, it will be necessary to examine this topic in greater detail.

The roots of the commodification debate

Commercial relationships have been viewed suspiciously throughout history. Commerce relates to objects solely on the basis of their value in trade, and this

252 Kant Immanuel. Fundamental Principles of the Metaphysic of Morals. In: Adler Mortimer J., editor. Kant. In: Hutchins Robert Maynard, editor in chief. Great Books of the Western World. Chicago: Encyclopedia Brittanica Inc.; 1952. p. 271.

253 "Man cannot dispose over himself, because he is not a thing. . Hence a man cannot dispose over himself; he is not entitled to sell a tooth, or any of his members". Cited in (29), number 27:460.

254 In his essay "Chartism", Carlyle repeatedly bemoans the fact that the market culture reduces all human relationships to the "cash nexus". Marx in section 4 of volume I of Capital outlines his theory of the "fetishism of commodities", whereby market valuation of production alienates us from the production and the producers alike.

255 Heschel, Avraham Yehoshua. Who is Man. Stanford: Stanford University Press; 1965.

method of valuation may lead to a diminished appreciation of other, more profound measures of value, whether inherent or utilitarian.

The concern for the social impoverishment incumbent on commodification became particularly acute in the early nineteenth century, as commerce became the dominant mode of human interaction in an increasing number of areas. This concern came from varying places on the political spectrum.

It is in this period that we find the Conservative thinker Thomas Carlyle bewailed that the dominance of a system of market valuation overturned traditional relationships of duty, in a period when "Cash Payment had not then grown to be the universal sole nexus of man to man".[256]

During the same era, Carlyle's Radical contemporary Karl Marx was expounding his theory of alienation and reification, in which relating to economic goods as commodities regrettably obscures the relationships between the worker on the one hand and the employer, the customer, and the product of labour itself.[257]

We see that the "commodification" of commodities themselves involves two main problems: one is the impoverishment of the relationship between man and object, and the other is the impoverishment of the relationship between man and man. In the ideal situation, I both appreciate the unique character of a particular object as well as its relationship to the individual who created it; when it is reduced to a commodity I relate to its monetary value and form no lasting bond with the producer.

As we apply these concepts to the commercialization of products of the human organism, the two dimensions become conflated: ownership of a particular human organ or human gene may inculcate a reductionist view of humanity in which a human being is little more that the sum of his or her marketable anatomic parts, causing us to lose sight of the unique, transcendental human value of the person created in the Divine image.

Is commodification truly the ogre we fear?

While the obligation to relate to others as independent ends is an ethical axiom, the assertion that commercial society violates this remains a conjecture. We have to ask exactly what aspects of this commerce are objectionable, and under what circumstances they may be appropriate.

What we seek is some concrete evidence that relating to something as a commodity indeed tends to degrade or cheapen our awe and respect for it. Certainly we cannot blame the spread of the market system for all human ills! There can be no doubt that despite Carlyle's nostalgia and Marx's triumphalism, decadence and exploitation both predate the market's rise and survived its demise.[258]

256 Carlyle Thomas. Chartism.

257 Marx Karl. Capital. Vol. I section 4.

258 That is, in those countries which adopted non-market alternatives to capitalism.

One could easily claim that the exact opposite holds: that it is precisely the commodification of a man's biological endowment, which enables us to esteem his spiritual essence in the purest fashion! In this scenario, the true villain is the holistic, pre-capitalistic mode of apprehension, which fails to separate a person's utilitarian, economic worth from his inherent spiritual worth. When the artisan was selling his labour, his trade was his identity and the aristocrat was his master twenty-four hours a day. But the proletarian selling his labour power becomes the equal of the plutocrat the moment he punches out of work at the end of the day.

The analogue to stem cell research might state that permitting property rights in human cells is a positive way of emphasizing that human worth is not a function of our mere biological constituents but rather of substantive participation in human consciousness and human society.[259]

If we were to examine this hypothesis, however, we would find ample evidence that commercial connections do indeed have a tendency to crowd out other types of interaction and esteem.

One demonstration that commodification can be demeaning is linguistic. Our vocabulary is replete with pejorative terms whose demeaning connotation stems solely from the commodification of some normally esteemed value. A soldier is the symbol of honour, a mercenary the symbol of contempt. And even a libertine who might admire a "ladies' man" disdains the "gigolo".

We can also find concrete behavioural evidence that commodification is considered degrading. We mentioned previously evidence brought by Richard Titmuss that at least some individuals are more willing to donate blood than are willing to sell it for small amounts. When people donate blood they feel they are serving an exalted human purpose, yet the identical act, which indeed serves the identical purpose, is debased in their eyes when it bears a salient commercial character.

Even so, we should acknowledge the theoretical distinction between commodification and degradation. And we can also point to those instances where commodification can constitute an elevation in status for a relationship that would otherwise be even more debased. A hired worker who sells his labour enjoys more status than a chattel slave who is bought for money but forced to work without recompense, and even this latter can look down on a prisoner in a press-gang.

This theoretical distinction should persuade us that the focus of our ethical attention should not be towards the extent of commodification per se, but rather the extent to which some kind of market relationship demeans or effaces some more exalted non-market relationship which would otherwise be present. One precedent for this kind of approach is the work of Margaret Jane Radin. Radin does not speak of a sharp demarcation between commodification and other kinds of valuation, but rather of "indicia of commodification". Furthermore, she points out that "Literal commodification and commodification

259 We find a fascinating parallel to this conundrum in the debate over the humanistic significance of the theory of evolution. It has often been averred that the belief that man is descended from the apes degrades man's unique spiritual status; yet the opposite claim has also been heard: it is precisely the theory of evolution which emphasizes man's ascent over his descent.

in conceptualisation need not be coextensive in practice, but they are loosely interdependent".[260]

Indeed, we can find an expression of this idea in Kant. In his Lectures on Ethics, Kant discusses the ethical prohibition on treating the human body as an object of commerce; in particularly he is objection to prostitution. Kant asserted: "Man cannot dispose over himself, because he is not a thing. He is not his own property - that would be a contradiction. Therefore, Kant reasons, "a man cannot dispose over himself; he is not entitled to sell a tooth, or any of his members."

Kant's lecture continues: "But now if a person allows himself to be used, for profit, as an object to satisfy the sexual impulse of another, if he makes himself the object of another's desire, then he is disposing over himself, as if over a thing, and thereby makes himself into a thing by which the other satisfies his appetite, just as his hunger is satisfied on a roast of pork. Now since the other's impulse is directed to sex and not to humanity, it is obvious that the person is in part surrendering his humanity, and is thereby at risk in regard to the ends of morality."[261]

Note that while in the first paragraph Kant opines that selling of organs is unethical, in the following paragraph he is focusing not on the money exchange per se but rather at the fact that the person is being used merely to satisfy the appetite of the other person. This seems to allow for the possibility of some kind of money exchange as long as the essence of the exchange is not purely exploitative.

Compensation and transformation of commodification

After we evaluate the potentially damaging ethical impact of commodification, we need some way of weighing this damage against the economic benefit which market relations can provide, which involve their own ethical value in reducing human suffering. After all, we have pointed out that even ordinary commercial relations involve some degree of instrumentalisation in human relations, yet we consider that the ethical benefits of free markets in advancing human freedom and providing for basic wants outweighs this blemish.

Ethically questionable exchange relationships can be validated in two distinct ways: compensation or transformation. In other words, the benefits from allowing such exchange may outweigh the conceded detrimental effect of commodification, or these benefits may actually vitiate these detrimental elements through a transformation of the nature of the ethical act.

An example of validation through compensation would be commercial sponsorship of cultural activities. Dependence on commercial advertising can adversely affect both the content and the context of popular entertainment, yet this trade-off has been considered worthwhile because of the immense

260 Radin Margaret Jane. Contested commodities: the trouble with trade in sex, children, body parts and other things. Cambridge MA: Harvard University Press, Cambridge MA; 1996:118.

261 Peter Heath and J.B. Schneewind, editors; Lectures on Ethics in the Cambridge edition of the Works of Immanuel Kant. Cambridge University Press, New York, 1997. Number 27:386.

resources commercial enterprises are willing to devote to popular culture in return for the ability to advertise, and because of the concrete benefits to sellers and consumers from the advertising itself.

An example of validation through transformation is military service. The unique social constraints on hostile acts by soldiers generally guarantee that they are viewed gratefully as servants of their country, not regretfully as unavoidable "hired killers".

Since avoiding a problem is better than overcoming it, we should strive to create a property regime in medical research in which the ethical benefits transform and elevate the commercial aspects to the greatest possible extent. This requires a careful examination of what properties successfully effect such a transformation.

While exchange relations can be transformed so as to co-exist with an essentially ethical act, this transformation requires certain restrictions on the scope of the market relationship. Indeed, the very fact that the public imposes restrictions because of its values automatically signals a non-market kind of valuation and diminishes the extent of commodification. Radin writes, "[L]aissez-faire markets represent complete commodification, and regulated markets represent incomplete commodification. Regulated markets represents incomplete commodification in a stronger sense in situations where they reflect internally plural meaning".[262]

In general, we discover that such transformation is facilitated when market relations are restricted in duration and scope.

Taking the example of military service, servicemen and women are required to make a long-term commitment unlike any found in civilian life; even the most dangerous tasks are not paid commensurately with what civilians are paid to assume such hazards; their hostile actions are subject to strict discipline and to the most rigorous limitations in order to maintain purity of arms.

We can find a precedent for these principles in the Hebrew Bible, which limits commodification by placing careful economic restrictions on certain kinds of trade. In the twenty-fifth chapter of Leviticus, we learn that neither land nor men should be viewed as mere commodities. Land, because "the land is Mine; for your are strangers and settlers with Me" (Lev. 25:23); men, because "they are My servants" (Lev 25:55). Yet trade in land and labour is not forbidden outright, rather it is limited in scope and duration. Land ownership is restricted through the Jubilee release and the Sabbatical year; slave ownership is limited through limiting servitude to six years and by forbidding demeaning service.

Extrapolating to the instance of medical research, the ethical difficulties in granting property rights in materials, techniques or devices could be partially overcome by practical and symbolic limitations on these property rights. Here is a list of limitations that could maintain the essential ethical character of the research while sustaining a place for market incentives to advance it:

262 Radin p. 116.

Limitations on the duration of patent protection are already a feature of these rights. Patents provide protection for a period of twenty years.

Certain restrictions on the kinds of inventions also exist already, including the restrictions on subject matter and the requirement for novel, non-obvious and useful inventions. Likewise, patent law already makes the crucial stipulation that patent protection is granted only when complete details of the invention are disclosed. Process patents are clearly less commodifying than product patents and so the ruling of the Canadian Supreme Court allowing only process patents on higher life forms has the salutary effect of vitiating commodification.[263]

Current patent law does not restrict limited, non-commercial research use of a patented technique; this loophole could be expanded to some kind of "fair use" criterion. Already many laboratories are willing to provide availability of proprietary materials to researchers as long as a material transfer agreement is signed.

Conducting medical research can be defined as a per se ethical act only if the principle objective of the research is for vital therapeutic goals. Regulations limiting the possible uses of patents could have the effect of guaranteeing that this objective remains foremost.

Since the objective of research is public benefit from any therapies or diagnostics developed, the ethical dimension of the research could be augmented by a provision for compulsory licensing of the invention when appropriate. Many countries already have such provisions; in other countries some degree of public research subsidy could be viewed as a kind of "quid pro quo" for the power to compel availability when necessary.

Note that not all of these goals need to be achieved by the patent law itself. For example, if the use of embryonic stem cells were limited by regulation to vital medical purposes, this would have the effect of transforming the character of IPR in these cells even if the patent per se was not limited to such uses.

Importance of public debate

Appropriate regulation and legislation can make a critical contribution to creating a humane intellectual property system with regard to stem cells and other human tissues. Although we do not envision in this paper altering the fundamental rules relating to patenting these materials, the overall regulatory environment has a profound impact on the public perception of IP rights in this area. We can identify a number of distinct loci of this impact:

Intellectual property may have the effect of encouraging research, which is ethically problematic from the point of view of bio-ethics or medical ethics. For example, it may encourage unwarranted use of embryos or encourage a lack of adequate informed consent. This implies the necessity of implementing specific regulations, which will effectively prevent unethical procedures.

263 The dissenting opinion in the judgment acknowledged this fact, but implied that commodification is objectionable only with respect to human beings, and that the current wording of the patent act is sufficient to avoid giving property rights in human beings. Reference (2) above, Section E of the dissent.

As Margaret Radin points out, the very fact that the public authority intervenes to limit the uses of a particular good makes a statement that this good is subject to public interests and is not purely a commodity. We added that the particular character of the limitations, such as limitations in duration, scope, and subject matter, can portray an image of a technology and an industry devoted primarily to human well-being, and this image may help counter any reductionist impression given by the marketplace activity.

Continuing in this vein, even if ultimately no legislation or regulation is adopted, there is critical importance in creating public debate on these topics. The very fact that intellectual property rights in human biology are candidates for regulation or legislation creates a healthy opportunity for public discussion and values clarification. This creates a clear mandate for policy involvement in order to shape not only any regulation but also in order to take maximum advantage of any public attention given to these vital ethical issues.

Conclusion

Patent policy is a fairly arcane area of legal research, yet it has surprising importance in the ethical debate over stem cell research. Since only patents enable private investments in this technology to be profitable, patent policy is critical in shaping the nature of this research.

Because scientists acknowledge that SCR has great potential to relieve human suffering, the role of patents in encouraging productive research has a prominent ethical dimension. In addition to a scientific analysis we need an ethical analysis as well as an economic one to see if this research fulfils our expectations.

Beyond the specific details of patent protection, the very fact of patent protection makes an important and authoritative public statement about the public standing of this research. It tends to place such research squarely in the sector of market activity. After all, patents are not granted for new methods of relieving poverty or, for that matter, for novel approaches to problems in bioethics.

Standard economic analysis can greatly help in studying the effectiveness of patent policy, but even in this area we need to take account of the important ethical motivations that act within the research framework. Research subjects need to be reminded that their participation is not only a means to increased economic profit but also to improve human well-being.

Our conclusion in this area is that current patent law is well-equipped to encourage productive research, as long as the law is carefully applied and patents are given only to truly patentable inventions whose extent is clearly defined.

Market forces can encourage not only productive activities but also destructive ones, such as the trampling of patients' rights. Carefully designed regulations can do much to align economic incentives with ethical ones, helping ensure

that informed consent is obtained from all research subjects including donors. It would be helpful if these regulations were framed in a way, which continues to give expression to the altruistic dimension of such participation.

Patents on human stem cells do tend to depict them as mere objects of commerce, but this tendency can be partially counteracted by careful attention to the details of protection. Regulatory limitations on the extent and subject matter of patents, as well as on the use of the resulting technologies, can help prevent unethical practices, and also makes an important statement about the continuing public interest in this field – a statement which gainsays the view that human tissues are commodities only and which invites public debate and interest in this topic. Such regulation can encourage a more holistic view of the value of this research without vitiating the role of private investment in moving research forward.

An ethical patent regime should encourage research which fulfils the promise of relieving suffering, discourage irresponsible treatment of research subjects, and also make a positive and humane statement about the place of medical research in our society.

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Human embryonic stem cell patents in the USA

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1 INTRODUCTION

Today the United States Patent Office grants patents that cover hES cells despite its official position against the allowance of patents that "embrace human beings." What exactly "embrace human beings" means is unclear. However, historical U.S. legal treatment and current administrative precedent indicate that hES cells, especially totipotent ES cells[264], should be banned from patentability because inventions that cover such subject matter may indeed embrace human beings. As science finds ways to convert sources of hES cells (SCNT) and perhaps pluripotent stem cells into living human embryos, what embraces a human being will likely expand. The destruction of embryos should not, therefore, be governmentally sponsored by either the EU or the U.S.A through product patents on such inventions. Other avenues exist to promote economic interests while retaining human dignity on a worldwide basis.

2 LEGAL HISTORY[265]

In the United States, the history leading to patents on human embryonic stem cells and germ cells fails to provide an adequate mandate for the issuance of patents directed to such subject matter. Since 1790, the U.S. Constitution has squarely placed authority regarding the extent of patentable subject matter in the legislature, but only up to the ill-defined point where individual liberties are threatened. In accordance with this authority, Congress has left the scope of allowable subject matter virtually unchanged and unlimited. Although common law interpretations of what constitutes "useful" patentable subject matter since then have provided moral limitations from as early as 1817, as the common law developed, fluctuating judicial attitudes have ceased to uphold these moral limitations. Even supplementary legislative actions in both 1930 and 1970 indicating that Congress did not consider the patent act alone as sufficient to protect certain living materials were held as insufficient to place limitations on patentable subject matter. In 1980, for instance, the Supreme Court deemed all things "created by the hand of man" effectively subject to patent protection, and in so doing invited the legislature to impose limitations on patentable subject matter as appropriate. As a result, now that advances in biotechnology have ripened a conflict, administrative policy that heretofore easily adhered to commonly held notions of decency have made way for patents on human embryonic stem cells and germ cells, which themselves may eventually, if not already, embrace human beings. In the absence of clear limitations on the

264 Pluripotent stem cells by definition are not able to develop into a new individual. However, it is not clear whether cells that have been considered pluripotent so far, are in fact totipotent; see: Hübner K,Fuhrmann G, Christenson LK, Reinbold R, De la Fuente R, Wood J, Straumss III J, Boiani M, Schöler HR. Derivation of oocytes from mouse embryonic stem cells. Science 2003; 300: 1251-6. See also Chapter 4, § 4.5.

265 This section relies extensively on Nathan Adam's history of US patents on life. See Nathan A. Adams, IV, Creating Clones, Kids & Chimera: Liberal Democratic Compromise at the Crossroads, 17 Notre Dame J. L. Ethics & Public Pol'y 71 (2003).

scope of patentable subject matter, what was previously thought of as morally abhorrent is today's reality and tomorrow's future. Because the history leading to patents on human embryonic stem and germ cells lacks a conclusive legislative mandate, the prevailing statutory interpretation endorsed by the courts leaves an impossible *laissez faire* utopia that lacks sufficient governmental protections by creating an environment where even patents such as these issue.

At its foundation, the history leading to patents on human embryonic stem and germ cells begins with the U.S. Constitution. It provides that "Congress shall have power…to promote the progress of science and useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."[266] The Patent Act of 1793 defined patentable subject matter as "any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement [thereof].[267] Apart from the substitution of the word "process" for "art"[268], this language continues to define the scope of allowable subject matter for a U.S. patent and has been broadly construed to incorporate nearly all subject matter.

Widely construed as such, this language provides virtually no boundaries against the injustices of an unregulated free market. Although U.S. common law originally embraced the idea of moral exceptions to patentable subject matter[269], it has unfortunately fallen out of fashion at the single most needy junction – the patenting of human beings, the single most appropriate case that for government intervention. From the early-nineteenth century until midway through the 20th century, U.S. courts withheld patents on inventions falling chiefly within two classes: (1) inventions used to defraud buyers, particularly medicinal products, and (2) machines used for gambling.[270] Although never overruled this so-called beneficial utility theory fell out of favour in the 1970s and has since been discussed primarily in dicta.[271] In fact, the United States Court of Appeals for the Federal Circuit (the only mid-level appellate court with jurisdiction over cases arising under the patent statute)

266 U.S. Const. Art. I § 8.

267 Patent Act of 1793, 1 Stat. 319 § 1 (1793).

268 This substitution was made in 1952, when Congress re-codified the patent laws. Pub. L. No. 82-593, 66 Stat. 797 (1952) (codified at 35 U.S.C. § 101). The U.S. Supreme Court has interpreted "manufacture" to mean " the production of articles for use from raw or prepared material by giving to these material new forms, qualities, properties, or combinations, whether by hand-labor or by machinery." Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980) (citing Am. Fruit Growers, Inc. v. Brogdex Co., 283 U.S. 1 (1931)). "Composition of matter" includes "all compositions of two or more substances and…all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powers or solids." Id. (citing Shell Dev. Co. v. Watson, 149 F.Supp. 279, 280 (D.C. 1957)).

269 Lowell v. Lewis, 15 F. Cas. 1018 (C.C. Mass 1817) (Story, J.). "The principle derives from an early British patent statute, which excluded otherwise patentable inventions that were "contrary to the law,…mischievous to the State, by raising prices of commodities at home,…or generally inconvenient." M. Bruce Harper, TRIPs Article 27.2: An Argument for Caution, 21 Wm. & Mary Envtl. L. & Pol'y Rev. 381, 413 (1997), quoting 1 Stephen P. Ladas, Patents, Trademarks, and Related Rights § 4 (1979) (ellipses in original).

270 Robert P. Merges, Intellectual Property in Higher Life Forms: The Patent System and Controversial Technologies, 47 Md. L. Rev. 1051, 1062-65 (1988).

271 Ernest Bainbridge Lipscomb III, Walker on Patents, 538-41 (1984) (citing Ex Parte Murphy, 200 U.S.P.Q. 801 (Bd. App. 1977); Application of Anthony, 414 F.2d 1383 (C.C.P.A. 1969)). But see Tol-O-Matic, Inc. v. Proma Prod.-und Mktg. Gesellschaft M.b.H., 945 F.2d.1546, 1552 (Fed.Cir.1991) (discussing Lowell in dicta) [hereinafter Tol-O-Matic].

recently stated that the beneficial utility doctrine "has not been applied broadly in recent years."[272]

An additional doctrine that has seemingly fallen by the waste side is the "product of nature doctrine." At least until the current Patent Act of 1952, "[d]espite the anomalous patent, such as that issued to Louis Pasteur in 1873 for his purified culture of yeast, the court invariably rejected patents that involved living subject matter."[273] The primary reason was that something could not be "new" if it already exists in nature.[274] One of the earliest decisions articulating this doctrine found the fibre within pine needles unpatentable:

> Even if…this were the first time that men had discovered that a fiber existed in the leaves and needles of the trees which could be…made useful for mankind, it is doubtful whether the invention would consist of anything more than the process by which the fiber could be taken from the natural leaf….Otherwise it would be possible for an element or a principle to be secured by patent, and the patentee would obtain the right, to the exclusion of all other entities of securing…the fiber which nature has produced.[275]

Although the product of nature doctrine is simple, judges have struggled to apply it consistently to distinguish patents over such products of nature *per se* from patentable processes that merely use or secure these products.[276] Until 1930, the PTO understood the doctrine to preclude the patenting not merely of animals, but also plants.[277] Congress addressed this concern and the inability of inventors to provide an adequate "written description" of plants in 1930 by passing the Plant Patent Act, which purportedly expanded patentable matter to certain varieties of asexually reproduced plants (*i.e.*, plants propagated by cuttings, grafting, and budding but not seeds).[278]

An explosion in plant breeding followed, which, together with the rise of pesticide and herbicide use, led to the Green Revolution. Sexually reproduced plants were not included in the Plant Patent Act of 1930, because, according to the U.S. Supreme Court, "new varieties could not be reproduced true-to-type through seedlings."[279] By 1970, Congress intended to resolve this perceived

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272 See Juicy Whip, Inc. v. Orange Bang, Inc., 185 F.3d 1364, 1366-7 (Fed. Cir. 2001) [hereinafter Juicy Whip].

273 David G Scalise & Daniel Nugent, Patenting Living Matter in the European Community: Diriment of the Draft Directive, 16 Fordham Int'l L.J. 990, 999 (1992-3); Sheldon Krimsky, Biotechnics & Society: The Rise of Industrial Genetics 46-47 (1991) (after Louis Pasteur received the first patent on a living organism in 1873 (e.g., purified yeast), nine additional patents issued on single-celled organisms from 1908 to 1925 (e.g., ground vegetable or animal matter inoculated with bacteria, bacteria mixed with cocoa, food product containing lactic bacilli, and micro organisms in vegetable oil)); Ryan M.T. Iwasaka, Note, Chakrabarty to Chimeras: The Growing Need for Evolutionary Biology in Patent Law, 109 Yale L.J. 1505, 1511 (2000).

274 Scalise & Nugent, supra note 10, at 999.

275 Donald S. Chisum, Chisum on Patents § 1.02[7][a], 1-30 to 1-34 (citing Ex Parte Latimer, 1889 Comm'n Dec. 13, 125-27 (1889)) (ellipses in Chisum, supra).

276 Scalise & Nugent, supra note 10, at 999-1001. See, e.g., Dennis v. Pitner, 106 F.2d 142, 143 (7th Cir. 1939) ('A discovery in the field of science of a new quality of phenomenon of an old product may be…the proper subject of a patent.").

277 Chakrabarty, 447 U.S. at 311-12 (PTO granted two patents stating claims for living micro organisms in 1967 and 1968).

278 Plant Patent Act of 1930, 35 U.S.C. § 161 ("Whoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber propagated plant or a plant found in an uncultivated state, may obtain a patent therefor….").

279 Chakrabarty, 447 U.S. at 313.

problem[280]therefore by also extending plant variety protection to novel strains of sexually-reproduced plants (except fungi, bacteria, or first-generation hybrids), rendering as patentable those major food crops that are developed through classical hybridisation techniques.[281]

This legislation, together with the Patent Act, provided the backdrop for the U.S. Supreme Court's groundbreaking Chakrabarty decision in 1980, holding oil-digesting bacterium as patentable.[282] Arguing for the opposite result, the government contended that, (1) bacteria were excluded from the Plant Patent Act of 1930; (2) the Patent Act did not apply to living things (as evidenced by the Plant Patent Acts of 1930 and 1970); and that (3) genetic engineering technology was unforeseen when Congress enacted the Patent Act.[283] Four Justices agreed, insisting that at least since 1930, Congress must have intended that the PTO not patent living organisms under the Patent Act; otherwise, plants could have been patented without the Plant Patent Act of 1930 and 1970.[284] They argued that Congress expressly excluded bacteria from protection under the Plant Patent Act of 1970, indicating its affirmative intent not to patent bacteria.[285]

The Chakrabarty majority disagreed, arguing that the relevant distinction Congress meant to draw under the Patent Act was not between living and inanimate things, but between products of nature (whether or not living) and human-made inventions.[286] The majority added that Congress merely presumed that the product of nature doctrine rendered this type of invention unpatentable.[287]

In time, the PTO and its administrative judges took the next steps toward patenting plants and animals. The Board of Patent Appeals and Interferences was the first to extend Chakrabarty by holding that non-naturally occurring, multi-celled plants are patentable under the Patent Act.[288] Then, the same body held patentable multi-cellular organisms known as polyploid oysters (non-

280 Since then the Supreme Court has ruled that the U.S. Patent Act indeed covers sexually produced plant varieties. J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc., 534 U.S. 124, 131-132 (2001) (holding that plant utility patents on sexually reproduced plants are "compositions of matter" under 35 U.S.C. § 101 despite, as admitted by the Court, Congressional belief in both 1930 and 1970 that utility patent protection was unavailable for sexually reproduced plants during enactment of the (now merely supplemental) Plant Patent Act and Plant Variety Protection Act).

281 Plant Variety Protection Act of 1970, Pub. L. No. 91-577, 84 Stat. 1547 (codified at 7 U.S.C. § 2402(a)) ("The breeder of any novel variety of sexually reproduced plant (other than fungi, bacteria, or first generation hybrids) who has so reproduced the variety…shall be entitled to plant variety protection therefor….").

282 Chakrabarty, 447 U.S. at 309 (1952). Chakrabarty, who worked worked for General Electric Company, applied for a patent with three claims: the process of making the microbe, a method of dispersal, and the organism itself. The PTO granted all but the last one. PTO's denial was on grounds that micro organisms are products of nature and living things are not patentable subject matter under 35 U.S.C. § 101. Id. at 305-06.

283 Id. at 310-11, 313-15.

284 Id. at 319-20 (Brennan, White, Marshall, and Powell, JJ., dissenting).

285 Id. at 321 n.3.

286 Id. at 313. The Court distinguished Funk Bros. Seed v. Kalo Inoculant, 333 U.S. 127 (1948), where the inventor produced no new bacteria, but merely combined existing species of root –nodule bacteria to inoculate seeds. "Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature…." Chakrabarty, 447 U.S. at 310.

287 Compare id. at 316, with id.at 305 n.2.

288 Ex Parte Hibbard, 227 U.S.P.Q. 443, 447 (Bd. Pat. App. & Interf. 1985).

naturally occurring oysters produced by making multiple copies of genes through hydrostatic pressure, not biotechnology).[289] Within days, the PTO announced that it would begin treating all non-naturally occurring, multi-celled organisms (animals) as patentable, except humans.[290] The PTO grounded the exception for humans on the unspecified constitutional objection widely assumed to be the Thirteenth Amendment.[291]

A year after the PTO announced this policy, animal rights organizations, farmers and others brought suit challenging it as an improper exercise of agency discretion in violation of the Administrative Procedure Act (APA).[292] They lost on at least two grounds, first, because the plaintiffs were held to lack standing because the patent statute did not grant members of the public the right to intervene in the prosecution of patent applications. Second, the plaintiffs could not demonstrate that the injury was proximately caused by the mere issuance (as opposed to use) of a patent.[293] The Court, moreover, reserved the question whether the PTO's exclusion of humans from patentability was substantive.[294]

The PTO, thus draws the line at human beings. This policy has been generally adopted by the PTO since at least 1987, when it announced it would begin treating as patentable non-naturally occurring, multi-celled organisms, excluding humans.[295] As justification for not granting patents on human beings, the Patent Office mentioned an unspecified constitutional limitation widely construed as the Thirteenth Amendment.[296]

The Thirteenth Amendment to the U.S. Constitution prohibits slavery and involuntary servitude. Thus, it seems that (the now former) Patent Commissioner, Quigg, treated this as why the U.S. Patent and Trademark Office could not issue patents on human life or part-human organisms even following the Chakrabarty decision, despite the U.S. Supreme Court's indication that "anything under the sun that is made by man" is patentable. With respect to human clones, some commentators accordingly agree that the Thirteenth

289 Ex Parte Allen, 2 U.S.P.Q.2d 1425 (Bd. Pat. App. & Interf. 1987), aff'd, 846 F.2d 77 (Fed. Cir. 1988) (holding multicellular animals patentable but rejecting the particular application made in this case for unrelated reasons).

290 See Comm'r of Patents and Trademarks, Policy Statement on Patentability of Animals, 1077 Off. Gaz. Pat. Office 24 (Apr. 7, 1987), reprinted in Donald S. Chisum, Chisum on Patents app. 24-2 to 24-3 (1998). Critics of the expansion of Chakrabarty to this extent note the progressively narrower forums in which decisions about patentability have been made from the legislature to the courts to the executive branch. See, e.g., Krimsky, supra note 10, at 48.

291 Id. See also Thomas A. Magnani, The Patentability of Human-Animal Chimeras, 14 Berkeley Tech. L.J. 443, 448.

292 Animal Legal Def. Fund v. Quigg, 932 F.2d 920 (Fed. Cir. 1991).

293 Id. at 929-30. On standing, the Court noted that third parties have no right to intervene in the prosecution of patent applications to prevent their issuance. Id. at n.9. And the Court rejected appellants' claims to have suffered injuries traced to the challenged action that could be redressed by a favourable action. Id. at 930.

294 Id. at n.9.

295 See Commissioner of Patents and Trademarks, Policy Statement on Patentability of Animals, 1077 Off. Gaz. Pat. Office 24 (Apr. 7, 1987), reprinted in Donald S. Chisum, Chisum on Patents app. 24-1 to 24-3 (1998) [hereinafter "Statement on Patentability of Animals"]. This announcement followed the Board of Patent Appeals and Interferences decision in Ex parte Allen, 2 U.S.P.Q 2d 1425 (Bd. Pat. App. & Interf. 1987), aff'd, 846 F. 2d 77 (Fed. Cir. 1988).

296 Statement of Patentability of Animals, supra note 3 at App. 24-1 ("The grant of a limited, but exclusive property right in a human being is prohibited by the Constitution. Accordingly, it is suggested that any claim directed to a non-plant multicellular organism which would include a human being within its scope include the limitation 'non-human' to avoid this ground of rejection.").

Amendment draws a line regarding what is, and what is not, an acceptable patent by precluding the creation of persons to be used as "spare parts" and by prohibiting reproductive cloning. [297]

Notwithstanding this administrative stance and the various policy reasons behind it, the U.S. legislature has left the patent statute unchanged so that it fails to draw such an explicit line, however, even after ratifying the first patent treaty to address such issues. Recently the United States ratified and implemented a patent treaty that sets certain minimum requirements for patent protection, but allows exemptions for immoral inventions. The 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) provides that members of the World Trade Organization, such as the U.S., may exclude from patentability "inventions, the prevention within their territory of …which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment."[298] The TRIPs agreement adds that members may exclude from patentability, "diagnostic, therapeutic and surgical methods for the treatment of humans or animals" and "plants and animals other than micro-organisms, and essential biological processes for the production of plants or animals other than no-biological and microbiological processes." [299] These exceptions in the TRIPs accordingly reflect the content of patent statues in most of the industrialised world outside of the United States. Many such statutes explicitly preclude the patenting of inventions "contrary to l'ordre public or morality."[300] Regional integration efforts have also adopted the ordre public exception, most importantly the European Union (EU).[301] While negotiating the TRIPs, however, the United States opposed incorporation of such ordre public or morality exceptions[302], albeit unsuccessfully, and has, in keeping with its earlier position, opted out of implementing such exceptions into the U.S. patent statute.

297 Lori B. Andrews, Is There A Right to Clone? Constitutional Challenges to Bans on Human Cloning, 11Harv. J.L. & Tech. 643, 668; Note, Asexual Reproduction and Genetic Engineering: A Constitutional Assessment of the Technology of Cloning, 47 S. Cal. L. Rev. 476, 517 (1974). Cf. Kevin D. DeBre, Patents on People and the U.S. Constitution: Creating Slaves or Enslaving Science, 16 Hastings Const. L. Q. 221 (1989) (granting of patent rights on chimera would not violate the U.S. Constitution, only certain exercises of these patent rights would be unconstitutional).

298 Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, § 5, art. 27(2) available at http://www.wto.org/english/ docs_e/legal_e/final_e.htm (on file with the Notre Dame Journal of Law, Ethics & Public Policy).

299 Id. art. 27(3).

300 See Patents Throughout the World (Alan J. Jacobs ed., 4th ed. 1996).

301 See European Patent Convention, Oct. 5. 1973, art. 53, available at http://www.european-patent-office.org/legal/epc/e/ar53.html ("European patents shall not be granted in respect of: (2) inventions the publication of which would be contrary to 'ordre public'or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the contracting States…."); Council Directive 98/44, art. 6(1) 1998 O.J. (L213) 13, 18 [hereinafter Directive] ("Inventions shall be considered unpatentable where there commercial exploitation would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation."); Japanese Patent Law, Law No. 121 of 1959, art. 32 ("The inventions liable to contravene public order, morality or public health shall not be patented…."), available at http://www.jpo.go.jp/shoukaie/patent.htm.

302 Harper, supra note 6, at 415.

As part and parcel of the resulting U.S. legal framework, the PTO issued the first patent on a multi-celled animal on April 12, 1988, also known as the Harvard Oncomouse[303], and regularly grants patents on numerous transgenic animals. Some of these patents cover spliced human DNA that express human hormones or other chemicals not otherwise produced by animals in nature.[304] The PTO also regularly allows patents on human cell lines and methods of deriving them, including, as of 2001, at least 1,000 patents covering gene research. Some of these would yield transgenic humans.[305]

The PTO has also issued a patent covering a procedure for cloning humans (and "products" thereof) through parthenogenesis.[306] Major newspapers reported recently that the U.S. Patent and Trademark Office issued U.S. patent no. 6,211,429 to the University of Missouri at Columbia on April 3, 2001, potentially providing the university and its licensee with property rights over cloning techniques and cloned mammals including, for example, human beings.[307] Notwithstanding the news, the stated position of the PTO continues to be that it will not grant patents on human life or any process leading to the creation of human life.[308] Thus, while the stated position of the PTO continues to be that it will not grant patents on human life nor even a process to create human life, the agency has publicly abandoned the Thirteenth Amendment as its reason.[309]

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303 Magnani, supra note 28, at 448.

304 Iwasaka, supra note 16, at 1532. By 1999, the PTO had received over 1,900 patent applications for genetically altered animals. Id.

305 Warren D. Woessner, The Evolution of Patents on Life –Transgenic Animals, Clones, and Stem Cells, 83 J. Pat. & Trademark Off. Soc'y 830, 844 (2001); Magnani, supra note 28, at 448; Neil Munro, The New Patent Puzzle, 34 Nat'l L.J. 628 (2002).

306 Andrew Pollack, Debate on Human-Cloning Turns to Patents, N.Y. Times, May 17, 2002, at A14; Antonio Regalado, Patent on Human-Cloning Method is Granted, Despite Current Policy, Wall St. J., May 16 , 2002, at D3 [hereinafter Regalado I]. See also Press Release, Patent Watch, The U.S. Patent Office (PTO) Has Granted a Patent on Human Reproductive Cloning and the Embryos, Fetuses and Children that Would Be Created Through that Process (May 16, 2002), available at http://www.patentwatchproject.org. At least three additional pending patent applications cover cloned human embryos and fetuses and an additional application would patent a human-mouse chimera, dubbed the humouse, and fuse human cells with those of a monkey, ape, or other animal. Id. (applications from Geron Corp., the University of Connecticut, and the University of Massachusetts cover cloned human embryos); Aaron Zitner, Patently Provoking a Debate, L.A. Times, may 12, 2002; Rick Weiss, Rifkin Files Human-Chimp Chimera Patent, Wash. Post, Apr. 2, 1998, at A12. The humouse application submitted in 1997 was initially rejected in 1999, because it embraced a human being.

307 Antonio Regalado, The University of Missouri Receives Patent of Human-Cloning Method, Wall St. J., May 16, 2002 [hereinafter "Regalado I"]; Andrew Pollack, Debate on Human Cloning Turns to Patents, N.Y. Times, May 16, 2002.

308 Pollack, supra note 43 ("Brigid Quinn, a spokeswoman for the patent office, said the agency was not using the 13th Amendment argument anymore but was not granting patents on humans because it had not received any guidance from Congress or the courts saying it should do so."); Regalado I, supra note 44 ("Our policy is that we do not issue patents to claims drawn to humans. Our policy has not changed."); Antonio Regalado, Ethical Concerns Block Widespread Patenting of Embryonic Advances, Wall St. J., Aug. 20, 2001, B1 [hereinafter "Regalado II"] ("A spokesman for the Patent Office says the agency not only forbids patents on human beings but also on any method for making them. The reason is that the owner of a patented "process" can prevent anyone else from importing products made using the technique. With cloning, that could lead to human clones born overseas being legally denied entry into the U.S."); Neil Munro, The New Patent Puzzle, Nat'l J., March 2, 2002 ("The U.S. Patent and Trademark Office does not issue patents drawn to human beings.").

309 Pollack, supra note 43 ("Brigid Quinn, a spokeswoman for the patent office, said the agency was not using the 13th Amendment argument anymore but was not granting patents on humans because it had not received any guidance from Congress or the courts saying it should do so."); Regalado I, supra note 44 ("Our policy is that we do not issue patents to

In lieu of the Thirteenth Amendment, the PTO resurrected Justice Story's beneficial utility theory as the rational why humans and chimera are not patentable, in April 1998:

> The PTO will not… issue a patent for an invention of incredible or specious utility or for inventions whose utilization is not adequately disclosed in the application. Additionally, the courts have interpreted the utility requirement to exclude inventions deemed to be "injurious to the well being, good policy, or good morals of society."…[T]he existence of a patent application directed to human/non-human chimera has recently been discussed in the news media. It is the position of the PTO that inventions directed to human/non-human chimera could, under certain circumstance, not be patentable because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement.[310]

As recently as April 1, 1998, the PTO reaffirmed this position in writing and added that human-animal chimera are generally unpatentable.[311] The PTO drew upon Justice Story's reasoning that inventions lack utility if they are "injurious to the well being, good policy or good morals of society.'"[312] Although the beneficial utility doctrine remains valid with a history of applicability to medical inventions, sceptics contend that the PTO is poorly suited to make normative judgments about biotechnology.[313] As mentioned moreover, the United States Court of Appeals for the Federal Circuit, the authoritative patent court , recently stated that the "beneficial utility doctrine has fallen out of favour" or "has not been applied broadly in recent years."[314]

Notwithstanding its policy, and perhaps in part because of the policy's shifting foundation, the PTO has thus allowed a number of patents involving embryonic stem cell lines, whereas (under a different patent regulatory regime) the European Patent Office purportedly has not. In the last year, patent applications in the areas of human embryonic cloning and ES cell research have jumped 300% in the United States. Critics contend that a backlog of applications is developing, because US patent precedent provides no useful guidance as to the standards for patent review for living organisms and no

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claims drawn to humans. Our policy has not changed."); Munro, supra note 45 ("The U.S. Patent and Trademark Office does not issue patents drawn to human beings."); Antonio Regalado, Ethical Concerns Block Widespread Patenting of Embryonic Advances, Wall St. J., Aug. 20, 2001, at B1. ("A spokeman for he Patent Office says the agency not only forbids patents on human beings but also on any method for making them. The reason is that the owner of a patented "process" can prevent anyone else from importing products made using the technique. With cloning, that could lead to human clones born overseas being legally denied entry into the U.S.").

310 Patent & Trademark Office, Media Advisory, Facts on Patenting Life Forms Having Relationship to Humans, (Apr. 1, 1998) (citations omitted), available at http://www.uspto.gov/web/offices/com/speeches/98-06.htm.

311 PTO, Facts on Patenting Life Forms Having a Relationship to Humans, April 1, 1998, Available at www.uspto.gov/web/offices/com/speeches/98-06.huml (last visited on march 8, 2002).

312 Id. (citing Lowell v. Lewis, Fed. Cas. No. 8568 (C.C. mass. 1817) Story, J.), quoted I Tol-O-Matic, Inc. v. Proma Product- und Marketing Gesellschaft M.b.H., 945 F.2d 1546, 1552 (Fed. Cir. 1991)).

313 See. e.g., Duane Nash, Recommended Response for Human Cloning Patent Applications, 42 IDEA 279, 297-98 (2002) (citing Robert P. Merges, Intellectual Property in Higher Life Forms: The Patent System and Controversial Technologies, 47 Md. L. Rev. 1051, 1062 (1988)).

314 See Tol-O-Matic, supra note 8; and Juicy Whip, supra note 9.

guidance as to whether a human being or partial-human organism (*i.e.* a chimera) is considered patent-eligible subject matter.

3 PATENTS COVERING HUMAN EMBRYONIC STEM CELLS

3.1. Claims that cover 'primate' and 'human' ES and EG[315] cells

The number of U.S. patents that now cover embryonic stem cells and germ cells is expanding rapidly. Such patents may or may not ultimately be held to cover humans, however. Despite their literal wording and breadth of claims, in some cases these patents contain only non-human data and/or altogether too specific descriptions. Many claims to embryonic stem cells for instance simply cover "primate" stem cells.

More specifically, U.S. class 435/325 includes claimed subject matter comprising the following:

> Animal cell, per se (e.g., cell lines, etc.); composition thereof; process of propagating, maintaining or preserving an animal cell or composition thereof; process of isolating or separating an animal cell or composition thereof; process of preparing a composition containing an animal cell; culture media therefore [sic].[316]

This class is subdivided into subclasses 435/325-408.[317] One of these subclasses, 435/363, covers "primate cells, per se"[318], and an online search of the USPTO database conducted on August 26, 2003 accordingly revealed that 138 patents fall under subclass 435/363, i.e., include claims to "primate cells, per se." Of these patents, 33 patents included "stem cell" or "germ cell" in the written description (i.e., the specification not including the claims)[319] and 7 patents include "stem cell" or "germ cell" in the claims. [320] Moreover, 5 patents include "embryonic stem cell" in the written description and 7 patents include "stem" or "germ" and either "embryo" or "embryonic" in the claims. Two patents specifically include "embryonic stem cell" in at least one claim. Some of these claims also specifically state that the embryonic stem cells covered thereby are human.[321]

Despite the above-mentioned contents of class 435/363, most claims to human embryonic stem cells or germ cells fall within class 435/366, which specifically

315 Referring to cells taken from foetal gonads.

316 USPTO Classification Schedule of Class 435 CHEMISTRY: MOLECULAR BIOLOGY AND MICROBIOLOGY, available at http://www.uspto.gov/go/classification/uspc435/sched435.htm.

317 Id.

318 Id.

319 The earliest of these patents is U.S. Patent No. 5,359,046 (issued Oct. 25, 1994) ("Chimeric chains for receptor-associated signal transduction pathways").

320 The earliest of these patents is U.S. Patent No. 5,670,361 (issued Sept. 23, 1997) ("HIV-specific Ribozymes").

321 See e.g., U.S. Patent No. 6,200,806 (issued Mar. 13, 2001) [hereinafter Thomson].

covers humans, however. A second set of searches specifically directed to human embryonic stem cells and germ cells revealed that many more patents specifically claim cells having a human origin than a merely "primate" origin. By way of explaination, the "primate cells per se" subclass (435/363) is divided itself into further subclasses 435/363 through 435/372.3, of which classes 435/366 through 435/372.3 cover only "human" cells.[322] Thus, subclass 435/366 purportedly contains all claims to human cells, including those cells not otherwise classified in classes 435/367-372.3.[323]

An online search conducted on August 25, 2003 of the USPTO database accordingly revealed that 953 patents fall under the "human" subclass, 435/366. Of these patents, 188 patents included "stem cell" or "germ cell" in the written description (i.e., the specification not including the claims)[324] and 41 patents include "stem cell" or "germ cell" in the claims.[325] Ultimately, 32 patents include "embryonic stem cell" in the disclosure and 24 patents include "embryonic" or "embryo" and either "stem" or "germ" in the claims. Of these 24, further analysis shows that all of these 24 patents have claims that require the use of either an embryonic stem cell or germ cell, and most specifically claim either an embryonic stem cell or germ cell as a positively recited claim element. Many of these patents further claim the cells themselves. Thus, at least 20 U.S. patents claim human embryonic stem cells or germ cells as part of a process or product.[326]

With regard to these 20 patents, most specifications contain human experimental data and specifically disclose at least two prophetic examples[327] of human subject matter to support the claims. However, the ultimate question is whether the above-referenced patents actually cover human embryonic stem cells.

In answering this question it is important to note that not all of the 20 patents found to claim human embryonic stem cells include data actually derived from the use of human embryonic stem cells. This situation likely poses an

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322 Id.

323 These subclasses designate a particular system or tissue type source. See, e.g., class 435/370 which includes cells taken from a human liver. USPTO Definitions of Class 435 CHEMISTRY: MOLECULAR BIOLOGY AND MICROBIOLOGY, available at http://www.uspto.gov/go/classification/uspc435/defs435.htm#C435S366000.

324 The earliest of these is U.S. Patent No. 4,963,489 (issued Oct. 16, 1990) ("Three-dimensional cell and tissue culture system.")

325 The earliest of these is U.S. Patent No. 5,556,783 (issued Sept. 17, 1996) ("Methods of culturing and modulating the growth of hair follicular stem cells").

326 These 20 patents include U.S. Patents Nos. RE37,978 (issued Feb. 4, 2003) ("Myocardial grafts and cellular compositions"), 6,280,718 (issued Aug. 28, 2001) ("Hematopoietic differentiation of human pluripotent embryonic stem cells"), 6,218,181 (issued Apr. 17, 2001) ("Retroviral packaging cell line"), 6,200,806 (issued Mar. 13, 2001) ("Primate embryonic stem cells"), 6,194,212 (issued Feb. 27, 2001) ("Vectors comprising SAR elements"), 6,140,121 (issued Oct. 31, 2000) ("Methods and compositions to improve germ cell and embryo survival and function"), 6,015,671 (issued Jan. 18, 2000) ("Myocardial grafts and cellular compositions"), and 5,843,780 (issued Dec. 1, 1998) ("Primate embryonic stem cells"). In addition to these 19 such patents found in subclass 435/366, the author found U.S. Patent No. 6,331,406 (issued Dec. 18, 2001) ("Human Embryonic Germ Cell and Methods of Use" is found in class 435/7.21, 435/375, and 435/377).

327 A prophetic example is a disclosed embodiment of claimed subject matter that remains untested, but may nevertheless prove to be a workable manifestation of the invention once it is actually reduced to physical practice.

enforcement problem with equal regard to both the enablement requirement[328] and the written description requirement[329] of the United States Patent Statute. Specifically, although both of these issues will arise during claim construction and patent validity, for the sake of determining patent scope, our focus will be on claim construction.

To be "enabled" such that a patent is judicially held to cover human ES cells, courts will apply the eight-factor Wands[330] test. Under Wands, a patent, including relevant deposited biological materials, must enable one skilled in the art at the time of invention to practice the claimed invention.[331] Specifically, a deposit of the relevant cell lines or other necessary components for practicing the invention may not be necessary "if the biological organisms can be obtained from readily available sources derived from readily available starting materials through routine screening that does not require undue experimentation."[332] For enablement, the principle inquiryessentially boils down to whether an attempt to practice the invention requires "undue experimentation."[333]

Data consisting only of non-primate examples, therefore, would seem likely to fail the Wands test because of the need for undue experimentation. For patents filed just a few years ago, researchers skilled in the art maintain that simply searching for ES cells in each new species remained a daunting job.[334] In addition, the process for deriving human ES cells differs substantially from such methods for mice and other non-primate species.[335] Claims supported only by non-primate data would therefore likely cover only non-human ES cells and germ cells.

Human ES cell and germ cell patents that include only non-human primate data might on the other hand suffice to meet the enablement requirement even without human data. If a court holds that disclosed non-human primate data would have been sufficient to enable one having ordinary skill to practice the invention at the time of its filing, the scope of the relevant claims could include human ES cells. In Amgen, Inc. V. Hoechst Marion Rousel, Inc.[336], claims to endogenous genes and exogenous genes alike were held enabled even though the patent contained only a discussion of the exogenous gene sequences. "Where the method is immaterial to the claim, the enablement inquiry simply

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328 See 35 U.S.C. § 112, ¶ 1.

329 Id.

330 In re Wands, 858 F.2d 731 (Fed. Cir. 1988) [hereinafter Wands].

331 Id. at 736.

332 Id. (footnote omitted).

333 Id. (Wands sets forth an eight-factor test to determine undue experimentation including: 1. The quantity of experimentation necessary, 2. The amount of direction or guidance presented, 3. The presence or absence of working examples, 4. the nature of the invention, 5. The state of the prior art, 6. The relative skill of those in the art, 7. The predictability or unpredictability of the art, and 8. The breadth of the claims.).

334 Antonio Regalado, The Troubled Hunt for the Ultimate Cell: Studies on the Human Embryonic Stem Cell, Tech. Rev., Jul. 17, 1998, at 37, available at LEXIS, News Library, Techrv File. (Further evidence exists in that mouse ES cells were the only ones isolated and purified for more than a decade.).

335 E.g., primate ES cells have an absolute requirement for feeder layers of irradiated fibroblasts in order to propagate in an undifferentiated state in vitro, while "Leukemia inhibitory factor (LIF) is necessary and sufficient to prevent differentiation of mouse [ES cells]." Thomson, supra note 58.

336 126 F. Supp. 2d 69 (D. Mass. 2001), aff'd in part, vacated in part, 314 F.3d 1313 (Fed. Cir. 2003).

does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed."[337] Thus, largely to the extent that methods for isolating and purifying non-human and human primate are the same, even claims to "primate" ES cells supported only by a disclosure of non-human examples may conceivably be held to enable coverage over human ES cells.

Similar chances for satisfying the written description requirement exist for such patents even despite the strict standard set forth in Regents of the University of California v. Eli Lilly & Co.[338] In Lilly, the patent appeals court[339] held a claim to human insulin cDNA invalid because the patent, although providing a method for isolating the DNA and describing the protein sequence of the insulin that the human cDNA encoded, did not describe the human cDNA itself. Further analysis in the case of human ES cells shows that some human ES cell patents may fail to disclose a written description (or deposit) of human stem cells themselves in the specification. Whether such a disclosure is sufficient seems largely addressed in the seminal Lilly case to the effect that such patents would be construed narrowly, to avoid a finding of invalidity for lack of an adequate written description.

Stem cell patents having only non-human primate data, but which disclose human stem cells and thereby support claims to human cells, might nevertheless meet the written description requirement even despite Lilly. Several recent cases seem to limit the applicability of the strict written description requirement set forth in Lilly v Regents.[340] The resulting trend for the patent appeals court to back away from Lilly, therefore, increases the likelihood that more and more early human ES cell claims, though unsupported by a human ES cell disclosure, will overcome the written description requirement and thereby be held to cover human ES cells.

As seen, patentees with patents not explicitly claiming human ES cells may succeed in their attempts to enforce their patents against those who use human ES cells, even where the patent merelt disclose non-human examples. This point is largely moot, however. Under current trends, which give little to no deference to the moral utility doctrine, human ES cells patents that do rely on human data (and that particularly describe human embryonic stem cells and methods for obtaining them in their specifications) will likely be construed to cover human embryonic stem cells under current law.

3.2. "Downstream" claims involving human ES or EG cells

In the same way that artful claim drafting presents an affront to human dignity in Europe, so it does in the United States. Innumerable present and future claims to processes that will doubtless require the destruction of human ES

337 Id.

338 119 F.3d 1559 (Fed. Cir. 1997) [hereinafter Lilly] (At a minimum, the CAFC thereby signalled that it will apply a heightened written description requirement to those biotechnology inventions involving DNA and genus/subgenus issues, for instance, involving vertebrate insulin cDNA/mammalian insulin cDNA.).

339 The United States Court of Appeals for the Federal Circuit.

340 See e.g., Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316 (Fed. Cir. 2002).

cells and germ-line manipulation will be claimed in U.S. and European patent applications, especially as technology develops. Even if claims to these processes artfully avoid an explicit mention of hES cells many patents will nevertheless require the destruction of human embryos. For instance, of just the published human and other primate applications that disclose "embryonic stem cell" to date[341], it is highly likely that a number of these applications will not explicitly claim an embryonic stem cell as part of a product or process, but nevertheless require the use of such cells to be practiced.[342]Herein referred to as "downstream claiming", such artful patent drafting will result from politically astute attempts to pass under politically opposition radar. As downstream technology develops, a particular invention, while necessarily requiring the use of a hES cell, may no longer need to explicitly claim or even disclose the acquisition of such cells to overcome the previously-mentioned written description and enablement requirements in order to adequately disclose and claim the invention.

The European experience with regard to the question of whether such patents are appropriate has been highlighted by what interpretation is to be given to the explicit exceptions to patentability set forth in the EU Biotech Directive. Lessons from the European experience, especially in the absence of public oppositions in the US, will resound again unless U.S. legislative policy says otherwise..

These lessons are briefly noted, beginning with an account of current European legislation regarding the topic. First of all, embryonic stem cell research using IVF embryos and cloning (somatic cell nuclear transfer, "SCNT"), whereby diploid donor DNA is placed in an egg which is electrically stimulated to become an embryo) is accepted in Britain through licensing.[343] By contrast, France and Germany have decided to ban it.[344] In Germany the extraction of stem cells from a human embryo is a crime, though it is legal to import cell lines.[345] In France, all human cloning, including for therapeutic purposes, will be prohibited in June, 2003.[346]

If European countries lift such bans, limitations on patent protection may be the sole step taken by governments at least to refrain from actively supporting the destruction of human embryos. Even if embryos or commercial uses of embryos are not themselves held patentable, however, downstream uses and products likely will be, especially if medical demand for embryonic stem cells outpaces the demand for adult stem cells. The same holds true for methods and products related to so-called "therapeutic" cloning and the modification of the human germ line.

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341 An online search, August 24, 2003, showed that 2541 such applications have been published by the US Patent and Trademark Office.

342 This number will likely increase as the technology advances, and so explicit downstream reference to hES cells as a starting material may not be as necessary. Nevertheless, more and more hES cells will be required to practice such inventions.

343 Mark Henderson, EU Curbs Threaten British Stem Cell Research, TimesOnLine, Mar. 29, 2002, at http://www.timesonline.co.uk/printFriendly/0,,1-2-626734,00.html.

344 Id.

345 Id.

346 Id.

Medical advances have been promised without anyone knowing for sure if they will indeed result, including cures for Alzheimer's, cystic fibrosis, Parkinson's disease, and paralysis (cf. chapter 2). Thus, according to the implicit ethical framework that underlies such assertions, it seems that "the ends" may be held to "justify the means." In other words, the underlying ethical assumption is that honourable, life-saving goals should be pursued according to any and every available method, even if such method itself threatens the very humanity it is employed to protect. This view epitomises a consequentialist ethical philosophy that does not take into account other important ethical points of view (cf. chapter 3).

Thus, the limits found in Article 6(2) of the European Biotech Directive may not ultimately exclude inventions that use human embryos, especially now that so many economic and death-defying aspirations tout these embryos as a modern-day fountain of youth.

In addition, legislative limits on patent enforcement will likewise fail toachieve the goals of those who oppose patents on hES cells. Placing limits on enforcement might never have its desired effect in part because commercial entities, if sued for infringement, are less likely than non-commercial opponents to overturn a patent based on more general moral grounds, perhaps for fear that their own hES cell patent portfolio would be rendered useless.[347] At least one author suggests that if moral questions were to be raised during enforcement, there would need to be some way to ensure "some adequate role for public participation in decision making of this kind."[348]

As a result, those who oppose hES cell patents in Europe feel powerless.[349] More specifically, "the democratic process is being replaced by a sort of expertocracy".[350] "[I]f we insist on leaving ethical and moral judgements concerning patents on life to the patent lawyers and the patent administrators, we cannot get a humane, compassionate set of decisions, but rather reductionistic and mechanistic ones."[351] These opponents to hES cell patents in Europe propose general and broadly written exclusions.[352] These statements,

347 Presentation of Daniel Alexander at the Int'l Workshop 'Biotechtechnology , Patents and Morality: Towards a Consensus' (Jan. 17-19, 1996), in Biotechnology, Patents and Morality, p. 254, 257-258 (Sigrid Sterckx ed., 2d ed., 2000) ("There are institutional issues … here…because one of the things that has generated so much trouble for the EPO is the fact that the opponents to patents of this kind are not commercial entities. From my experience, which is primarily dealing with commercial litigation, they quite often have an interest in keeping well quite about certain of the activities of even the people they are suing for patent infringement or being sued by. The [true] opponents of this kind are people who, as it were, have no interest in the matter commercially.")

348 Id.

349 Dani De Waele, The Virtual Reality of the Biotechnology Debate, in Biotechnology, Patents and Morality, pp. 188-189 (Sigrid Sterckx ed., 2d ed., 2000).

350 Presentation of Jan Mertens at the Int'l Workshop 'Biotechtechnology , Patents and Morality: Towards a Consensus' (Jan. 17-19, 1996), in Biotechnology, Patents and Morality, p. 247, 247 (Sigrid Sterckx ed., 2d ed., 2000).

351 Presentation of Steve Emmott at the Int'l Workshop 'Biotechtechnology , Patents and Morality: Towards a Consensus' (Jan. 17-19, 1996), in Biotechnology, Patents and Morality, p. 250, 252 (Sigrid Sterckx ed., 2d ed., 2000).

352 Id. at 252-253 ("such a statement of the law, as we think it should be… It is already signed by hundred's of NGO's and thousands – if not tens of thousands – of individuals. I will read it to you, as it is very short:
The undersigned organizations and individuals oppose the granting of patents on genetic material, originating or derived from humans, animals and plants. We believe that the extension of patent law to the basic genetic structure of living matter means treating life itself as a mere commodity, with adverse moral and practical consequences for humankind, the animal kingdom

even if incorporated into the Directive verbatim, will not fully achieve their intended purposes.

Similar opposition exists in the United States, but with a comparatively much smaller and less vocal opposition group. In addition to patents mentioned from U.S. class 435 above, patents covering untold numbers of processes that use human ES cells and that manipulate the human germ-line, have and will issue.[353] Other patents that claim necessary constituents of human embryonic stem or germ cells also appear on the horizon.

4 PATENTS THAT ILLEGALLY EMBRACE HUMAN BEINGS

As mentioned, the official policy of the USPTO states that no patents may embrace a "human being". What the USPTO means by the phrase "embrace a human being" is unclear. Nevertheless, this limitation alone constitutes the scant recent precedent available. One known case that illustrates USPTO policy is the Rifkin case, wherein a patent claiming a human-mouse chimera, among other creatures, was rejected on the basis that the beneficial utility doctrine prohibits the patenting of compositions that embrace a human being.

With the Rifkin precedent, as well as other legal precedent, in mind, pluripotent embryonic stem cells and certain germ cells (here understood as cells obtained from 8-9-week-old foetal gonad tissue, not gametes) might in the future also be held to embrace human beings. Legally, at least totipotent embryos embrace human beings even if they are not legal "persons."

While it has been argued that Roe v. Wade irrefutably stands for the proposition that an embryo is not a person,this definition is inapposite for the present case because in this case a woman's right to privacy fails to factor in. Plus, Roe involved a constitutional limit on governmental power, while in the present case, the issue is whether public policy demands at least some limitation on unfettered capitalism. Disallowing a patent in no way disallows an activity, it merely takes away explicit government sponsorship of runaway and, at times enslaving, market forces.

Much of the current language used in reference to this issue is unfortunately skewed. Language in this debate, such as what constitutes a "human being", therefore, is critical to its outcome. As things stand, inasmuch as cloning is concerned, much of the prevalent language in this debate already assumes that embryos from which stem cells, or germ cells, originate are not human

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and the natural environment. There is presently no unequivocal bar to patenting life forms. We believe that the following should be declared to be unpatentable as being contrary to public morality:

1) humans, human parts, human tissues and all genetic matter originating or derived from human sources;
2) processes and techniques for genetic modification of such human matter and methods, treatments and therapies for applying such processes and techniques;
3) animals, animal parts, animal tissue and processes for the genetic modification of animals;
4) plants, seeds, plant tissue and other propagating material.

I believe that only by excluding living material from patentability can we ever finally resolve the morality issue.").

353 See. e.g., class 424 covering "Drug, Bio-Affecting and Body Treating Compositions" http://www.uspto.gov/go/classification/uspc435/defs435.htm#C435S366000 (References to Others Classes IV).

beings. For example, media reports widely distinguish 'therapeutic cloning' from 'reproductive cloning.' Implicit in this distinction is the overt suggestion that 'therapeutic cloning', as opposed to 'reproductive cloning', does not involve the reproduction of a human being, whereas obviously the cloning step is identical in both cases.

Several "pro-choice" periodicals such as the New York Times have perhaps unwittingly adopted this language despite its tendency to draw a distinct, yet when thoughtfully observed, imaginary and unprincipled line between two points along the same developmental course of the human embryo. On the other hand, it is not surprising that these media frame the issue after the majority of "pro-choice" medical ethicists. Many ethicists who argue for embryonic stem cell research towards 'therapeutic cloning' reject the notion that once an early stage embryo is used, later stage foetuses also may well be destroyed to harvest therapeutic cells. They rather adopt the position that there exists a meaningful distinction between early embryos (about 15 days old) and nearly full-term foetuses. It is doubtful if these ethicists can identify, let alone agree, on a point at which the use of embryos, whether obtained through fertilization or through SCNT, becomes impermissible. Ironically, the only distinction they make seems to lie in whether our intention is to allow the embryo to live, (i.e. 'reproductive' cloning), or die (i.e. 'therapeutic' cloning), and not in a physical reality.

One "pro-choice" voice of dissent, however, is Stuart Newman. Dr. Newman, a developmental biologist, who is known for his strategic application for a patent claiming human chimera, opposes both of these types of human cloning, basing his reasons on a 'slippery slope argument,' i.e., that if human embryonic stem cells are used and patented from therapeutic cloning, then so will embryonic germ cell lines, and also ultimately full-term foetuses. His partner Jeremy Rifkin asks, at what price? "Even if you take the position that a human being isn't a human being until the first breath, you still have to say that at conception, when the sperm and egg come together, it's a potential human being," he says. "Then the question is, can a company own a potential human being, from conception through gestation to birth, as intellectual property? If that doesn't raise one of the great social issues in history, I don't know what does." Semantics aside, both sides of the "right-to-life"/"pro-choice" debate recognise that great ethical implications are at stake.

This reality is perhaps no better-illustrated than by the PTO's rejection of Dr. Newman's chimera patent. As stated, Dr. Newman's Chimera, which is not even completely human, has been held by the PTO to embrace a human being. If a chimera is considered human then, perhaps after future technical advances, a pluripotent stem cell will have the capacity to form a full-grown person, and likewise embrace a human being.

This conclusion alone should cause the US to ban patents on hES cells. After all, a 'potential human being' is worth more to society than a yet to be discovered 'potential medical breakthrough.' One advocate of federally funded embryonic stem cell research, who while primarily limiting her discussion to pluripotent stem cells, mentions that totipotent stem cells have the capacity to

develop into a fully functioning organism.[354] Nevertheless, this author continues just two paragraphs later by stating, "[w]ith the potential to alleviate or even cure diseases, stem cells are a miracle in the works." To be certain, these "miracles" refer to the promise of cures and treatments for our medical ailments, but this author fails to highlight the miracles of new life, e.g., (1) the creation of a human being and (2) the process whereby such a human being becomes a fully functioning organism and member of society.

What makes this statement noteworthy is its ironic tendency to persuade us in fact to outlaw totipotent stem cell research – even despite its author's intent to pursuade us to fund such research. Many advocates of embryonic stem cell research (and ultimately each therapeutic application thereof) claim that the enormous potential for curing diseases outweighs the necessary destruction of embryos. Several reasons exist, but one such reason minimises the rights deserved by these cells by deeming them merely "potential human beings" (but in effect not yet human beings, at least not to the extent that they should be given rights or defended as such.) As illustrated by the above-mentioned author's statements[355], it is seen that many proponents of embryonic stem cell research prefer a potential cure to a "potential human being."[356] Not only should we, therefore, disagree with the conclusion that an embryo be withheld protections that we who have voices enjoy; we disagree with the notion that a "potential human being's" life should be traded to extend our own lives (cf. chapter 3).

Yet, strangely all of the above-mentioned patents have issued. The resulting confusion may be caused by a lack of administrative oversight or more likely, a cloud of organizational inertia coupled with the economic incentives of a vested elite.

5 HUMAN DIGNITY AND THE MARKET

Indeed, the economic factors that drive hES cell patents in the United States are very similar to those driving such patents in Europe. The history of the European Union Biotech Directive[357], for example, again well illustrates the economic forces behind ES cell patents in the United States.

The European Commission deems implementation of the European Biotech Directive as quite urgent because of the traditional purpose of the patent system to provide incentives to bring goods to market and the increasingly important purpose of patent in a knowledge-based economy. The European Commission web site states the following reasons for the Directive:

354 Note, Dipping Into Uncle Sam's Pockets: Federal Funding of Stem Cell Research: Is It Legal?, 11 B.U. Pub. Int. L.J. 229 (2002).

355 Id.

356 Even if we assume that totipotent cells are merely "potential human beings," no one disputes that such cells can in fact become human beings. No "potential" medical cures, however, exist to date, and no such cures are guaranteed from the therapeutic use of totipotent stem cells.

357 Council Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, 1998 O.J. (L 213) 13.

> Why are patents necessary in the area of biotechnology? Patents provide an incentive to innovation. Without the safeguard provided by patents, industry and other inventors would be unwilling to invest their time and money in research and development. This applies to biotechnology as well as any other area of technology. Indeed given the considerable amount of risk investment that is often required in the area of biotechnology, particularly in the field of genetic engineering, adequate patent protection is even more essential to encourage the investment required to create jobs and maintain the European Union's competitiveness in this crucial field. Indeed, the key role of adequate patent protection in the creation of a dynamic; knowledge based economy was explicitly underlined by the March 2000 Lisbon Summit conclusions….This is why Directive 98/44 on the legal protection of biological inventions was proposed and, after lengthy and thorough discussions within the European Parliament and among Member States, adopted.[358]

In other words, because there is such a large pie at stake, individual companies want to secure predictable and certain biotech patent protection to make their products as profitable as they can. The estimated value of the European biotechnology market is expected to reach over 100 billion Euro by 2005.[359]

Moreover, the institutions of the European Union, and especially the Commission, seem obsessed with their role in challenging the United States for economic pre-eminence. Within the context of the Biotech Directive debate, this aspiration rings crystal clear. For example, the Commission has been very active in the last year in its attempts to encourage member states to implement the Directive.[360] Most recently, the Commission has urged and threatened Member States to implement the Directive or face action in the European Court of Justice.[361]

Therefore, it is not surprising that since the Directive's 1998 enactment date, the European Commission ("Commission") has undertaken several steps to encourage implementation of the Directive by the EU member states. In accordance with Article 16(c)[362] of the Directive, in October 2002, the Commission published its first annual report on the Directive's status to the Parliament and Council.[363] This report emphasized the urgency of

358 Legal Protection of Biotechnical inventions: Frequently Asked Questions on Scope and Objectives of the EU Directive (98/44), July 3, 2000, at http://www.europa.eu.int/comm/internal_market/en_indprop/invent/2k-39.htm, (last viewed on Mar. 31, 2003).

359 Jelena Markovic, EU Members Urged to Respect Biotech Inventions Protection, World Markets Research Centre Daily Analysis, Oct. 11, 2003, at 2002 WL 104042264.

360 The European Commission has published its first annual report on the development and implications of patent law for biotechnology, Food Chemical News 27, November 4, 2002, at 2002 WL 118800024.

361 Nations Could Face Court Action Over Biotech Patents, Eur. Drug. Rep., Jan. 13, 2003, at 2003 WL 10105423. (The nine nations charged with second and final warnings known as "reasoned opinions" are Austria, Belgium, France, Germany, Italy, Luxembourg, the Netherlands, Portugal, and Sweden.)

362 Directive, supra note 38, art. 16(c), at 24.

363 Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering: Report from the

implementation, especially in view of the long-passed July 2000 deadline for such actions.[364] It highlighted four key aspects of the Directive: compatibility with international agreements, patentability of plants and animals, patentability of elements isolated from the human body, and exclusions from patentability provided in the Directive.[365] At the report's release, European Internal Market Commissioner Frits Bolkestein stated that "unless the 1998 Directive is properly implemented, Europe's biotech sector will be working with one hand tied behind its back and will fall further and further behind."[366]

In addition, the Commission has set up an ethics group, in accordance with the Directive, to consider and report on various ethical issues raised in the debate. It has recently published suggestions regarding appropriate interpretations of the specific issues regarding embryonic stem cell patents.[367] Likewise, the Commission has set up a legal, economic, and technical group[368] to consider and report on the various legal, economic, and technical issues implicated by the future trends in commercial biotech research and development.[369] This latter group is undertaking two topics, the first being the patentability of sequences and partial sequences of genes, and the second being the patentability of human stem cells and cells derived from them. The Chairman is Mr. Vincenzo Scordamaglia. The reporter for the first topic to be discussed in March 2003 is Sven Bostyn, and the reporter for the second topic to be discussed in May 2003 is Geertrui van Overwalle. The group is expected to come to its first set of findings in the summer of 2003 and publish these findings towards the end of 2003.[370]

It is important to note that the Directive is also only one part of a European Union goal to become the premiere global economic beneficiary of the biotech boom. Well outside of the Directive per se is the larger Commission plan to

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Commission to the European Parliament and the Council, COM(02)545 final at 1 et seq [hereinafter Development].

364 Id. ("All Member States must fully and swiftly implement Directive 98/44/EC on the legal protection of biotechnological inventions or Europe will fall behind its competitors in this crucial sector, damaging its overall efforts to become the most competitive economy in the world.")

365 The European Commission has published its first annual report on the development and implications of patent law for biotechnology, Food Chem. News 27, Nov. 4, 2002, at 2002 WL 118800024.

366 E.U. Nations Failing to Apply Biotech Patents Directive, Eur. Drug. Rep., Oct. 21, 2002, at 2002 WL 12316369.

367 EU Bioethics Group Opposes Stem Cell Patenting, Chem. Bus. NewsBase P9, Jun. 26, 2002, at 2002 WL 22910196 ("The bioethics group believes that unmodified stem cells should not be patented. It thinks that a European stem cell bank for unmodified cells should be created and made freely available to all. If the European patent office accepts these recommendations then all that will be patentable will be those processes generating stem cells or stem cell lines that have been modified. The recommendations differ significantly from US permit the patenting of unmodified cells. The bioethics also proposes that it should not be permissible to patent processes for creating stem cells by cloning techniques (therapeutic cloning which involves cell nuclei from somatic cells being inserted into denucleated egg cells) because this infringes the biotechnology directive of 1998.").

368 European Commission Press Release, Legal Protection of biotechnological inventions: Commission discusses progress with Member States and establishes expert group, Jan. 28, 2003, at http://www.europa.eu.int/rapid/start/cgi/guesten.ksh?p_action.gettxt=gt&doc=IP/03/127|0|RAPID&lg=EN&display=, (last visited Apr.1, 2003) [hereinafter EC Press Release].

369 Biotechnology – Commission Pushes For Implementation of Invention Protection Directive, Eur. Drug Rep., Jan. 29, 2003, at 2002 WL 10438886;

370 Id.

make the European economy the best in the world.[371] Accordingly, the Commission just published its report, "Life Sciences and Biotechnology: A Strategy for Europe."[372] Now the European Parliament has backed this position in a resolution that takes what has been seen as a "surprisingly biotech-friendly stance, rejecting more environmentally hard line arguments from the Greens."[373] All together, the Commission will fund biotech research at 2.225 billion Euro between 2003 and 2007,[374] and E.U. Trade Ministers met as the Competitiveness Council to endorse raising overall spending on drug R&D from 1.9 currently to 3.0 percent of GDP by 2010.[375] As seen, the economic goals of private industry and the Commission are the main driving forces behind the apparent desire to abandon meaningful ethical restrictions in the Directive.

Peter Drahos at the Queen Mary Intellectual Property Institute in London describes this unwillingness to assimilate and transfer ethical standards into patent subject matter restrictions as resulting from two structural problems.[376] The first is that increased worldwide standards gives knowledge-based economies (*i.e.*, in the U.S., Europe, and Japan) increased market share for their nationally-based industries resulting in increased exports.[377]

The second structural bias has to do with promoting "dynamic efficiencies based on technological innovation." For these "dynamic [economic] efficiencies" to continue, he asserts, investment in innovation has to continue. "There is no doubt that investment is 'the critical determinant of long-run economic performance."[378]

Therefore, by excluding all but the most absurd (and commercially nonviable) ethical restrictions[379] on patent law, a state achieves two things. First, it allows a broader range of patents, and second, it streamlines the content and administration of an already expensive legal area,[380] thereby enhancing the efficiency of its legal system in terms of who best protects innovation. This effect, in conjunction with a global democratisation of finance[381] causes

371 See Life Sciences and Biotechnology – A Strategy for Europe: Commission Communication COM(02)27 final at 1; see also Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering: Report from the Commission to the European Parliament and the Council, COM(02)545 final at 5.

372 Id.; see also, EC Press Release, supra note 103, Jan. 28, at 6 at http://europa.eu.int/comm/biotechnology/pdf/com2002-27_en.pdf.

373 Id.

374 E.U. Sets Out Roadmap for Biotechnology Development, Eur. Drug Rep., Dec. 2, 2002, at 2002 WL 123164429 [hereinafter Roadmap].

375 Biotech Roadmap Will Boost Competitiveness, Council Says, Eur. Drug. Rep., Dec. 16, 2002, at 2002 WL 12316438.

376 Peter Drahos, Biotechnology Patents, Markets and Morality, 21 Eur. Intell. Prop. Rev. 441, 446 (1999).

377 Id.

378 Id.

379 E.g., Hormone Relaxin, 1995 O.J. E.P.O. 388 (Opp. Div.), P 6.2.1 [hereinafter Relaxin] (Article 53(a) of the EPC "is likely to be invoked only in rare cases, for example that of a letter bomb.").

380 Patent prosecution and litigation is notoriously expensive. See Jean Eaglesham, "Pop-up tents refuse to give way: PATENT LITIGATION: Ninja Corporation's legal battle demonstrates the problems of enforcing rights against large corporations," Financial Times (London), August 13, 2001, at Inside Track Law & Business; Pg. 10; see also, Mark Horne, "Patent Costs," San Francisco Chronicle, July 18, 1988, at C3, col.3.

381 Thomas L. Friedman, The Lexus and the Olive Tree 101-142 (1st ed., Anchor Books 2000) (Democratisation of finance is exemplified by the emergence of both the "golden straight jacket," which forces governments to enact laws to attract

competition among states to create the most stable, reliable, and cost-effective patent system possible. As a result, each state has an incentive to adopt such patent systems.

Other states, in turn, risk a lot by not following suit, thereby creating a race to the bottom. To simply free ride off of the other state's technological advances would encourage diversion of money away from the second state to the first state. Over the long run, this would also reduce the second state's technological ability to copy, i.e., free ride, and all of the other advantages associated with technological superiority. For example, free riding would certainly reduce capital expenditure for research and production of non-patentable products, and thereby reduce job-producing industries. Therefore, "none of these [administrative] offices [or legislatures] can be seen to be weakening the patent system in any way. To do so would be to imperil investment flows in the territory for which the patent office [or legislature] has responsibility."[382,383] In accordance with these biases, even despite proposed government spending on research,[384] the European Federation of Pharmaceutical Industries and Associations (EFPIA) said that "spending more on research is fine. But without a system that rewards innovation, prospects for industry's ability to innovate and to discover medicines will not be enhanced."[385]

It's funny how money has a way of changing things.[386] Tony Blair presents a unique example. On March 14, 2000, while heralding the progress on the international human genome project, President Clinton and British Prime Minister Tony Blair spoke about sharing the genome code for the public good.[387] The perceived implication was that patents should not cover genes.[388] The result was a twenty-five percent drop in the total market value of the biotech industry. Despite every politician's desire, to voice sentiments that

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investment, and the "electronic herd," which comprises a new breed investors having the tools and appetite (an absence of national loyalty) to quickly move capital between countries.)

382 Drahos, supra note 111.

383 See also, Jelena Markovic, European Council Urges Review of Biotechnology Directive, World Markets Research Centre Daily Analysis, Nov. 19, 2002, at 2002 WL 104062293 (To wit, "the European Council is calling for more investment in the biotechnology sector… and a recent Council report has called for a review of current regulations… The report has…recommended… a review of the patentability of human stem cells and cell lines, as well as some gene sequences, which would allow Europe to gain an edge on US research.").

384 Roadmap, supra note 109.

385 Id.

386 Wallstreet (Paramount Pictures 1987) ("You know Bud, the thing about money is it makes people do things they don't want to do.").

387 Christina Wise, Investor's Bus. Daily, Mar. 15, 2000, at B10 ("A statement from President Clinton and U.K. Prime Minister Tony Blair favouring the free exchange of human genome data triggered the biotech sell-off. Though analysts termed the statement "political posturing," and noted that companies' patents to genes they have cloned remain intact, investors didn't care. Biotechs dove 13.2% on average. In all, the group has fallen 29% in six straight days of losses.").

388 John T. Bentivoglio & Martha L. Cochran, Policy issues could have major impact on industry, The National L. J., Jun. 25 2001, at C9 ("If there was any doubt that changes in intellectual property laws could have a dramatic impact on the value of biotechnology companies, that doubt was put to rest when then-President Clinton and British Prime Minister Tony Blair, speaking at a press conference to herald progress on the international human genome project, implicitly questioned whether human genes should be patentable. Their comments triggered near-panic selling of biotech stocks. The White House quickly issued a statement clarifying that the president was not suggesting a change in IP laws.").

resonate with emotional truths held dear by his or her constituency, it is likely that Mr. Blair thought the human genome should in some capacity remain part of what opponents to gene patents call our "common genetic heritage."[389] Whatever Mr. Blair's motives that day, he had an acute awareness of an ethical reality, which prompted his and President Clinton's excited response.[390] Since then recent discoveries have heightened hopes that cures for diseases such as Alzheimer's, Parkinson's disease, and cystic fibrosis may become possible by harnessing stem cells taken from human embryos. Of course, these ends are wonderful per se, but they also represent new sources of revenue in the health care industry. Not coincidentally, Mr. Blair now spearheads Europe's most aggressive campaign to promote embryonic and SCNT stem cell patents.[391]

It is ironic that Blair's gut-level comments likely played the most important role in the substantial drop of biotech venture capital investment from 2000 to 2001 in Europe.[392] Careful analysis of the Commission's first report on the Directive, which at first blush might otherwise lead an uninformed reader to believe that Directive non-implementation was the cause of the significant drop in venture capital in Europe between 2000 and 2001 after a decade of healthy growth,[393] reveals rather that Mr. Blair's comments probably account for the drop.[394]

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389 More Patents on Life Set to Go Ahead – Greenpeace Demands Scrapping of EU Patent Directive, October 5, 2000, at http://archive.greenpeace.org/~geneng/highlights/pat/00_10_05.htm, (last visited on Apr. 2. 2003).

390 Biotech executives have been working double-time to explain these remarks. See, e.g., Luke Timmerman, Gene patents preoccupy biotech execs, attorneys: Bio 2001, The Seattle Times, Jun. 27, 2001, at E1 ("But biotech execs say that the public misunderstood Clinton and Blair, and that the statements didn't mean the companies were relinquishing any parts of the genome they've patented.").

391 Innovation with Controls, M2 Presswire, Jan. 16, 2003, at 2003 WL 4564529 (The head of the UK's efforts to rationalise a morally suspicious approach through heavy regulation stated, "We look in detail at three controversial areas of research: seed and plant breeding, embryonic stem cell research, and nanotechnology. The UK is a world leader in embryonic stem cell research and has attracted millions of pounds of investment to this country and some top quality researchers from around the world. They benefit from a regulatory environment that is clear and precise."); see R (on the application of Quintaville) v. Secretary of State for Health. [2003] UKHL 13, [2003] All ER (D) 178 (Mar), (Approved judgement). (Blair's strategy is being thoroughly propped up by this recent and quite cynical decision by the House of Lords.).

392 BIOTECHNOLOGY Firms At Biotech Show Look Beyond Genome Project, Investor's Bus. Daily, Jun. 27, 2001, at A5 ("Skittish investors dropped shares after former President Clinton and British Prime Minister Tony Blair said gene libraries should share their data. Investors interpreted this to mean companies may not profit from their proprietary databases. Since then the sector has recovered, though not to its 2000 highs.").

393 Development and Implications of Patent Law in the Field of Biotechnology and Genetic Engineering: Report from the Commission to the European Parliament and the Council, COM(02)545 final at annex 5, statistics, Fig. 1 : EU VC investments in the Life Sciences sectors in millions of Euros.

394 Tom Abate, BUSINESS 2000: THE YEAR IN REVIEW; Of HUMAN genes, and Glowing bunnies and TAINTED tacos, S.F. Chron., Dec. 25 2000, at D1 ("Unfortunately, Wall Street misconstrued the leaders' remarks and thought they were moving toward abolishing all gene patents, which provide the legal foundation for most biotech therapies. Biotech stocks plunged, losing more than 15 percent of their value overnight.").

With specific regard to the economics of embryonic stem cell and germ cell patents, moreover, an example of so-called therapeutic cloning serves to illustrate the economics potentially at stake in the United States. If, for example, therapeutic cloning were simply banned in the US (and thus curtailing the enforcement of, and perhaps even the patenting of, inventions derived therefrom) the following scenario may occur. If so-called "therapeutic" cloning ere banned, it could turn out that innovations resulting from SCNT and ES cell research are so effective that the demand for them in the US is great despite thepresumed criminal ban on their development. It is very likely, so the argument goes, that other countries would allow therapeutic cloning research, as well as patents derived there-from, but because the US wouldn't allow such research, US law would in effect preclude foreign patent holders from enforcing their patent rights in the United States.

Without such constraints on competition in the US market, market entrants would therefore undoubtedly appear. Although some would try to provide a stem cell therapy as an illegal service in the US, it seems that more market participants would attempt to make money by running an over-seas clinic or by importing various therapeutic cell lines into the US in a sort-of-'mail order' fashion. In this later case, patients or a medical professional of choice might use a kit to extract DNA-laden cells and mail said cells (with or without an egg) to a foreign laboratory that uses that patient's DNA and an egg (from various sources) to grow tissue. After the healthy tissue is grown, it would be sent to the consumer in the US for therapeutic insertion/treatment at a local clinic.

This hypothetical argument also states that the first Brownback-Landrieu bill in the Senate, which would make the importation of such tissues illegal, would likely cut off the American market entirely and thereby force Americans who want such 'therapies' to travel to foreign countries to receive them. Thus, a host of healthcare jobs and shareholder profits derived from basic research, therapeutic services and related hospitalisation and surgery would be lost to the rest of the world. Plus, because of their high cost, overseas therapies such as these would be cost prohibitive for all, save a select few.[395] As seen in this scenario, the United States industry potentially looses out on the entire market - from drug companies, to auxiliary medical device companies, to medical practice groups, staff healthcare professionals, and even insurance companies. The argument concludes that this departure of industry from the US economy would keep at least one source of potentially lifesaving treatment from the majority of its population.

If adult stem cell technology, however, proves just as effective and develops with the same overall momentum as embryonic stem cell technology, prospects for US-based companies, workers, individual shareholders, and patients would be much better. And if in fact, adult stem cell technology ends up surpassing embryonic stem cell research, benefits to US entities and patients would be largely the same as if embryonic stem cell research had not been subject to any ban at all.

395 These costs would include travel, overnight and perhaps long-term hospital stays without ready access to places of work, and high costs without benefit of European national healthcare subsidies or US-based insurance that covers such treatment. Perhaps a new segment of the insurance industry would develop in Europe to provide coverage to US citizens for such therapies.

Nevertheless, the argument proposes the counterpoint that no matter how promising adult stem cell innovation, to bolster our economy we need to insure that domestic industry is allowed to benefit from all innovation. In other words, the US needs to refrain from government intrusion and thus diversify our investments by having at our disposal results from both adult and embryonic stem cell research. This can only be accomplished by allowing the patentability of ES cell research innovations. So goes the economic argument that opposes limitations on patentable subject matter.

Limitations on certain patentable subject matter, by contrast, strikes a balance between these opposing concerns by providing a mutually beneficial position. Because one job of government includes protecting its people from the dehumanising cruelties of Adam Smith's invisible hand, a middle ground between outright banning and full-fledged market dominance can be struck by banning certain ES cell patents. If ES cell patents are banned, then a government merely removes its own explicit and powerful sponsorship, thereby striking a healthy middle ground between economics and human dignity.

6 THE EU BIOTECH DIRECTIVE AS A MODEL FOR CROSS-NATIONAL SOLUTIONS

Turning once again to the familiar context of the European Biotech Directive, the situation in Europe well illustrates the need for legislation in the United States that would prohibit patents on human ES cells. In addition to the prevailing influence of market forces, and the disparity between intrinsic and consequential moralities, it should be noted that several of the particular arguments heretofore espoused by much of the biotech community are flawed. Opponents to ethical restraints on patentability argue that patents are to be kept immune to ethical considerations because patents are 'ethically neutral.'[396] Another stated reason is that patents only give a right to exclude[397], as if to say that, exclusive property rights are completely separate from ethical considerations. Finally, patent administrative agencies are not equipped to handle ethical decisions.[398] These arguments purportedly give a basis that clears the way for efforts of the European Commission, as well as for the European business, research, and patent community it seems, who seek to broaden patentable subject matter as widely as possible, despite the grave ethical implications.

From its inception, the Directive is a legislative creation, designed to promote the harnessing of technology by commercial enterprise - as the elected legislature deems fit. If a legislature wishes to protect all technology, it may. Such a situation exists where government sponsorship oftechnologies is desired, or at least acceptable to the public, because the public believes that morally permissable experimentation and useful products will result. In the same vein, if an elected legislature instead wants to exclude a particular subject matter, and thereby seek a middle ground by neither prohibiting nor sponsoring a particular technology, it should.[399] A much harsher result would be to prohibit the exploitation of a technology altogether. Such a measure could stop nearly all research. Therefore, when a new technology implicates ethical questions of unprecedented gravity, the legislature's hands are not tied.

Moreover, just because patentable subject matter is considered according to the same standards (e.g. novelty, non-obviousness, written description), once it is considered morally permissable does not make patents 'ethically neutral' per se. Technology is not ethically neutral. It is on the basis of ethics that governments exclude particular inventions from patentability based on the public's desire, or lack thereof, to grant state-sponsored incentives. Only after a technology falls within the ambit of legal patentable subject matter, does the constructive fiction of ethical neutrality, vis-à-vis the legal requirement for technological neutrality, come into play. This is because the legislature or rulemaking administrative agency has already made its one-time, winner-take-all decision regarding morality. Certain biotechnology is unique, and therefore

396 Tade Matthias Spranger, Ethical Aspects of Patenting Human Genotypes According to EC Biotechnology Directive, 31 IIC 373-380, 379 (2000).

397 See, e.g., Crespi, supra note 7.

398 See, e.g., Crespi, supra note 8.

399 This conforms to the prevailing international substantive patent treaty. See 1995 Agreement on Trade-Related Aspects on Intellectual Property Rights, Sept. 27, 1994, art. 27(2).

can and should form the basis for legislative exceptions to patentable subject matter. Why else would there be such a strong opposition by members of the public? The question of ethics in patents is a policy issue, pure and simple.

Because patents give a right to exclude, they are valuble property rights that invoke critical ethical questions. Using a real property analogy, a patent is like one right in the bundle of rights of a land holder. Except for very rare instances, law enforcement officials will allow a landowner to occupy and use his or her land. Sometimes, however, a law enforcement official might exclude everyone, including the landowner, from using the land, such as when it is a matter of public safety.

Whether the owner can use his land or not is not the land's only source of value, however. Another of the owner's right's is his right to exclude others from trespassing, whether he himself can use the land or not. When he can use it, this right is extremely valuable, because he has the right to exclusive use. When no one can use the land, this right to exclude is not as valuable.

But this is not the case with patents. Just as a patentee's right to exclude another's sale of his product is valuable, conceivably to the same extent there is value in this same patentee's right to exclude another's attempts to sell a product even if the patentee himself cannot sell such product. This is particularly true in the context of pharmaceuticals, for example. In cases where a patentee cannot prove that his drug is safe and effective, but perhaps a competitor, who has simultaneously developed the same patentable chemical moiety, can, this right to exclude is extremely valuble.

Accordingly, once a government sponsors capital investment by allowing patents on a particular technology, the wheels are set in motion such that investors have strong incentives not only to conduct research, but also to market a product and make a return on their investment, even if that product is harmful to the public. Therefore,suggesting that it is inappropriate to bring the concept of "property ownership" into the gene patent debate, [400] begs the following question: why do clients want patents so badly in the first place? The ethical questions that patents present cannot be ignored.

These ethical questions can be successfully addressed by Congress. Referring again to Europe, for example, taking the European Biotech Directive's ethically restrictive provisions seriously need not present severe administrative hurdles if the Directive is re-written to specify exactly what is, and what is not patentable. The same is true in the United States. Because patent officials do not have the ethical expertise or resources, they need guidance from a legislative body if the ethical restrictions are to be administered in a meaningful way. Thus, administrative hurdles are currently problematic, but not necessarily so, as long as Congress provides the necessary guidance to address the ethical implications that human embryonic stem cell patents present.

Exceptions to patentability are not new. They include few items, but nevertheless, exist. Patents on nuclear weapons and medical treatment

400 See Crespi, supra note 9, at 34 ("I suggest that bringing the concept of "property ownership" into the gene patent debate is inappropriate and leads nowhere as far as patent law is concerned.").

methods[401] are disallowed in many European nations. If a legislature finds that certain types of inventions and their related downstream inventions should not be government sponsored, perhaps a creative statutory scheme could be devised that allows all subject matter to be claimed, but does not allow such subject matter to be 'enabled' unless its practice could use non-restricted subject matter. For example, in the case of human embryonic stem cells, a patent would be granted but "constructively non-enabled" for a method or innovation that necessarily or practically requires the use of tissue derived from an embryonic stem cell. If the same method first conceived using an embryonic stem cell could effectively be used by using an adult stem cell, the patent then would be "constructively enabled," and thereby become enforceable. Although such a legislative device might ostensibly deter would-be patentees from developing and patenting human ES cell technology, it would heighten research regarding adult stem cell technology so as to "constructively enable" early patents developed using hES cells. It would also encourage other innovators to develop adult stem cell technology in the hope that they might obtain a patent that blocks the "constructively enabled" first hES cell patent. At this point any one could still use embryonic stem cell methods without fear of being sued, but the presence of mutually blocking patents would encourage the two patentees to cross-license, thereby activating both patents. This scenario would allow the two patentees to be the first ones to realise exclusive rights for what was originally, but no longer simply, human embryonic stem cell technology.

Finally, the larger argument that opposition to certain patents on ethical grounds is merely philosophical, more than anything only shows an at best naïve, and at worst, insidious refusal to acknowledge a divergence in ethical philosophies and value systems (e.g., between intrinsic and consequentialist ethics). In truth, both are philosophies. The first has been described as more speculative, but it lacks the degree of taint present in the latter by virtue of the latter's economically corrupting bias. All things weighed equal, therefore, neither of these value systems can be discredited out of hand nor dismissed as being outside of the voting public's widely held political ideology (cf. chapter 3.2). Any contrary argument is closely related to the losing argument that simply asserts that patents are inherently ethically neutral. Let the legislature decide, and not just a group of invested elites.

Several United States Congressional leaders have accordingly sought to avoid stepping over the bounds of common decency by statutorily banning the issuance of patents on human life and chimera.[402]

Specific precedent for this exists in the United States Code, which places limits on patents in technology specific areas. The United States Congress specially regulates another dangerous technology besides hES cells: atomic energy. The Department of Defense (DOD) reviews patent applications pertaining to atomic energy to decide whether an invention has weapons-related uses.[403] If the invention has only defence applications, DOD is entitled to all rights of the

401 Anna Feros, Patentability of Methods of Medial Treatment, 23 Eur. Intell. Prop. Rev. 79, 79-85 (2001)

402 Amendment to Prohibit Patentability of Human Life Forms, 107th Cong., 2d Sess. (May 2002).

403 See 35 U.S.C. §§ 181-88 (1982). Under this provision, the PTO must review all patent applications for military application. Id. § 181.

invention in exchange for just compensation.[404] Patents may not be issued at all to private parties on inventions useful solely for atomic weapons.[405]

With respect to medicine, U.S. patents are separately unenforceable in relation to "medical activity" defined as "a medical or surgical procedure on a body." The statute defines "body" (rather unhelpfully) as a "human body, organ or cadaver, or a non-human animal used in medical research or instruction directly relating to the treatment of humans.[406] One commentator argues a "human body" should not mean a living human embryo and that a human cadaver should not be subject to the statute.[407] Nevertheless, living, breathing persons are not the only ones given this respect under the patent statute. Even dead humans get special treatment, as should all living ones. Of course,with reference to Mr. Drahos' above-mentioned global racquet, and in keeping with Thomas Nash's famous game theory[408], industrialised countries, namely the three participants in the Trilateral Cooperation[409], must work together to limit ethically unconscionable patents, even though they compete with one another.[410]

7 EUROPEAN MEASURES

The first step that Europe can take to influence United States and Japanese law is to initiate in talks with the United States and Japan the goal and method by which they would jointly pass legislation to prohibit claims over human ES cells. Of course, Europe itself must be willing to undertake such steps. One preferred route would be to prohibit human ES cell product claims. In addition, certain process claims might be prohibited. To maintain additional incentives such a prohibition could be augmented by a constructive enablement provision such as the one suggested above, whereby claims requiring human ES cells would become enforceable as supplemental technology no longer requires the destruction of human embryos to be practiced.

A second strategy would involve current renegotiations of the TRIPs. Outlawing the patenting of human ES cell innovations internationally could be viewed as an economic benefit for Europe and the US if the EU and United States Trade Representative ("USTR") use it as a concession during negotiations over Intellectual Property Standards under the GATT. Thus, with specific regard to the economic argument for patenting ESC innovations, not only the USPTO, but perhaps even to a greater extent the USTR and various foreign Ministers of

404 42 U.S.C. § 287(c)(2)(A) (2000).

405 42 U.S.C.A. § 2181(a) (1994).

406 Id. § 287 (c)(2)(E).

407 Nash, supra note 50, at 302.

408 Made famous in the movie "A Beautiful Mind." This concept is also known as the prisoner's dilemma, wherein two conspirators may choose either jointly to receive a year long prison term if they remain quiet, or place the other in jail for 10 years so that he himself may go free.

409 See Trilateral Cooperation web site at http://www.uspto.gov/web/tws/gen.htm. This Cooperation is between United States (USPTO), European (EPO), and Japanese (JPO) patent authorities.

410 Precedent for this was achieved when the Group of Eight issued the only moral censure ever against live-birth cloning. Gina Kolata, Cloning: The Road to Dolly and the Path Ahead 228-229 (1998).

Trade, collectively comprise a strategic linchpin towards successful implementation of such global reaching laws.

As mentioned, not only is human ES cell research a moral issue; it is an economic one. European and the United States governments owe a duty to taxpayers not only to 'do the right thing', but also to promote their respective economies. Therefore, under the TRIPs the EU and US might find it economically advantageous and morally acceptable to bargain away their ability to patent hES cell innovations in return for stronger global patent protection in terms of other subject matter. This goal could be accomplished for example by requiring that all WTO countries allow patents covering business methods and software. Along this same vein, the U.S. and the EU could bargain for enhanced measures to ensure less burdened, more efficient and more just courts in other countries, and as a result better worldwide intellectual property protection for all other, ethically acceptable innovations. By leading a movement to ban the patenting of hES cell inventions, the EU and the U.S. will not only earn them greater favour and respect in emerging economic countries; from the overall U.S. and EU economic perspective, such a 'concession' might be used as a way to obtain enhanced protection of other Western produced intellectual properties in developing markets.

The context for such negotiations would be the TRIPs. The TRIPS, which was recently renegotiated last December during the Doha round and which was slated to be subject to negotiations in Cancun, inter alia, to extend the grace/phase-in period for various developing countries, sets minimal international protection standards for patents. This treaty is the first agreement that does more than simply require national treatment for patents. It sets international standards that require, e.g., a 20-yr term and more importantly to our concern, equal protection of innovations without any regard to scientific field. As stated above, however, exceptions are allowed based on morality.

It also allows compulsory licensing where a patentee otherwise refuses to meet domestic demand. During the Doha round, the US found itself outvoted by 140 to 1 on the issue of whether there should be compulsory licensing of patented drugs also to allow production for export to especially needy countries. As reported by Intellectual Property Owners:

> U.S. HOLDS OUT AGAINST ALLOWING COMPULSORY LICENSING OF PATENTED DRUGS FOR EXPORT AND ANNOUNCES MORATORIUM ON TRIPS ENFORCEMENT
>
> On Friday at the World Trade Organization in Geneva, after months of negotiation, the United States maintained its position as the lone holdout to an agreement for compulsory licensing of patented drugs for export to developing countries. The current TRIPS agreement allows compulsory licensing only when it is predominantly for the domestic market. The U.S. insisted that compulsory licensing for export must be limited to drugs to treat infectious epidemics such as AIDS, malaria, and TB. A U.S. list covering 23 such diseases was not accepted. The impasse means the WTO will not meet its Dec. 31 deadline for agreement on implementing the 2001 Doha Public Health Declaration.

> Late Friday the U.S. Trade Representative (www.ustr.gov) announced that as an interim measure the U.S. will observe a moratorium on using WTO dispute settlement procedures to prevent compulsory licensing for export "to help poor countries get access to emergency life-saving drugs." (Wall Street Journal, World Trade Online and USTR web site)

It was likely difficult for the US to stand alone on this issue. In fact, just recently, the U.S. conceded that compulsory licenses of patented drugs can in certain dire medical instances be extended to go beyond production merely for the relevant domestic market.[411] In effect, compulsory licensees in countries such as India or Egypt may also receive governmental licenses to produce and sell drugs beyond the domestic needs, to satisfy epidemic needs in African markets where drug production facilities do not exist. Thus, the point of all this is to raise question of how the EU and the rest of the world can affect US policy with respect to patenting hES cell research innovations.

As seen, rallying the world against the US position can be accomplished given sufficiently compelling reasons.[412] In this case, such a circumstance might prompt the U.S. to concede on this issue. Thus, one goal might be to raise the perceived threat to human dignity as nearly as possible to the level occupied by the threat of such diseases as AIDS in Africa.

Of course, this is a daunting task. Nevertheless, if such an opposition could be mustered, together (1) the EU, (2) traditionally minded nations who overwhelmingly oppose hES cell patents, and (3) U.S. non-healthcare patent holders may provide the political clout to internationally outlaw hES cell innovation patenting – a goal that would reduce domestic economic losses described in the hypothetical above. In addition to developing and other foreign countries who may wish to exclude human life forms from what may constitute patentable subject matter, US patent holders outside of the healthcare industry may prove to be strong allies for promoting such a concession. As a result, US patent holders in the healthcare industry may once again have their back against the wall. Therefore, perhaps not only moral interests, but also perhaps economic interests could be leveraged in the international community and with non-healthcare patent holders. These economic interests will dovetail nicely with the overriding moral and philosophical reasons to outlaw the patenting of human ES cell innovations.

8 CONCLUSION

Current United States administrative policy mandates that Congress outlaw patents covering human beings. The United States Patent and Trademark

411 See Symptomatic Relief, The Economist, Sept. 4, 2003.

412 Even more recently, the group of 22 lead by countries such as India and Argentina, walked out on the Cancun round of WTO trade negotiations over EU and US farm subsidies thereby showing the combined strength of many of the more traditionalist countries who can also be expected to oppose global patent protection of hES cell technology. See Cancun's Charming Outcome, The Economist, Sept. 20, 2003.

Office ("PTO") has stated that patenting human life, e.g., in the form of human clones and processes covering their creation, is illegal because it would necessarily violate fundamental human rights or lack beneficial utility. For example, the PTO has stated that giving a patentee the right to restrict the importation of 'goods' manufactured using a claimed cloning process would thus improperly conflict with the individual right of the cloned person to cross the borders of the United States of its own accord. Thus, the PTO has viewed the classification of a cloned person as a 'good' as an improper violation of that person's basic human dignity.

Because using totipotent embryonic cells (and pluripotent cells that may turn out to be totipotent after all)[413] requires the destruction of human embryos, the patenting of these cells and of any invention derived from them would also violate human rights. In fact, explicit government sponsorship via patenting ES cells would cause greater harm than simply violating a person's right to travel or cross US borders to the dignity given to others. It would violate a human being's fundamental right to live. As such, reasons substantially stronger than those underlying the PTO's prohibition of the patenting of human life exist for a similar prohibition by the PTO on claims directed to human ES cell research. Along this same thread, just as the PTO has banned claims to human life[414], even more so should Congress prohibit the patenting of human ES cells, but economic realities remain a powerful driving force.

Therefore, given the reasons underlying the PTO's standing prohibition of patents directed to human life and human rights violations inherent to ES cell research mandate that prohibitions be placed on patenting inventions derived from ES cell research. Because Congress, which the agency looks to for guidance,[415] has so far declined to rein in a robust young biotech industry with a habit of making generous campaign contributions, Europe should take a prominent role in the matter. Not only should the EU enact its own specific legislation and thus amend the Biotech Directive, it should join forces with the U.S., Japan, and the larger international community to outlaw the patenting of human ES cells.

413 See supra note 1.

414 The patent office rejected Dr. Stuart's chimera application in March 1999. In addition to citing moral grounds, the patent office declared that the chimera violated Quigg's rule because it "embraces a human being." (cf. supra notes 48, 49).

415 The patent office has made it clear that it resents being "dragged into a controversy which, from our particular perspective, we don't need to be a part of," as Stephen Kunin, deputy assistant commissioner for patent policy, told a legal magazine in 1999.

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