Europäische Akademie

zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen
Bad Neuenahr-Ahrweiler GmbH

Direktor:
Professor Dr. Carl Friedrich Gethmann

Embryo Experimentation in Europe

Bio-medical, Legal,
and
Philosophical Aspects

Minou Bernadette Friele (ed.)

February 2001

Grey Series Nr. 24

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Foreword

The Europäische Akademie Bad Neuenahr-Ahrweiler GmbH is concerned with the scientific study of the consequences of scientific and technological advance for individual and social life and therefore, not least with the study of consequences of recent developments in life-sciences and medical disciplines. The Europäische Akademie intends to contribute to finding a rational way for society to deal with the consequences of scientific and technological development. This aim is mainly realised by developing recommendations for options to act focussing on long-term social acceptance. The work of the Europäische Akademie mostly takes place in temporary interdisciplinary project groups, whose members are recognised scientists from European universities. In addition to these projects, workshops are taking place to provide a platform for intensive discussions on different related topics.

In the light of recent developments in molecular biology and reproductive medicine, the Europäische Akademie Bad Neuenahr-Ahrweiler organised a workshop on ”Embryo Experimentation in Europe” in June 2000. Experts from biology, jurisprudence and philosophy from different European countries were invited to discuss current scientific development, related questions of their moral implications and how to regulate new biomedical techniques, considering the differences between already existing national legislation and morals in the context of the project of harmonisation of the European Union.

The workshop focussed on two different but related fields of Embryo Experimentation:

– Biological, legal, and ethical aspects of cloning and stem cell research, and
– legal and ethical aspects of prenatal diagnosis (PGD).

With this volume of the Grey Series the Europäische Akademie aims to present the papers discussed at the workshop and, at the same time, to be a foundation for further investigations of scientific, legal and ethical aspects of embryo experimentation. The Europäische Akademie plans to continue working on this project within the scope of an international interdisciplinary project group.

Bad Neuenahr-Ahrweiler, February 2001

Minou Bernadette Friele, M.A.

Project Manager

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1. Introduction

Recently developed technologies enable scientists to culture and manipulate human embryonic cells. This has stimulated debate regarding the legitimate aims of and the extent to which experimentation on human embryos is scientifically desirable and morally acceptable.

On the one hand, advocates emphasise that (1) the allocation of rare organs and allogeneic transplantation with all their problems, like permanent shortage of transplantable organs and continuous use of immunosuppressive drugs, will be avoidable very soon by using stem cell therapy and that (2) in reproductive medicine by using preimplantation diagnosis (PGD) or cloning it might be possible to enable couples to avoid having children with genetic defects.

Given that surplus embryos from IVF treatments are routinely destroyed anyway and, more importantly, unable to suffer or form life plans, it is argued that there are no good reasons against using those embryos for research to develop new kinds of treatment against severe and widespread diseases and injuries.

On the other hand, critics emphasise that the success of these new techniques cannot be ensured and that expectations are often overestimated. From a moral point of view, the critics claim, there should not be any destructive research on human embryos for whatever scientific end because the moral status of the embryo excludes this categorically. Besides misgivings with regard to research on human embryos, it is argued that cloning and particularly PGD might lead to a new kind of eugenics.

This debate on how to treat human embryos covers fundamental questions of when personal human life begins and to what extent intervention in human reproductive capabilities should be permitted.

Although this debate is far from reaching its conclusion, research on human embryos has already started in many countries so that there is a pressing need to deal with questions of how to regulate such practices.
At the present time regulation of embryo research differs from country to country. Even in the European Union some countries prohibit it altogether, whereas others permit it to varying degrees or even do not have

any legislation at all on this topic. This leads to further problems that have to be taken into account. With respect to the project of the harmonisation of economy and legislation in Europe, and the practice of patients being able to seek help wherever they find it, we have to ask whether regulation on these topics should remain in the national sphere or if there is a need for legal regulations on a supranational level. Also here we must deal with the pros and cons: the advocates of regulation on the national level claim that values and underlying legal regulations differ from country to country and make a common regulation impossible while the advocates of regulation on a supranational level emphasise that national regulations are not sufficient for the reasons given above.

Attempts to develop a regulatory framework for bioethical questions in Europe have already been made, but have not yet been fully successful. For instance the *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine* (1996) has not been ratified by all states because in some aspects of it neither a consensus nor a compromise could be found. One of the main reasons why the convention is still not ratified by all European countries is a disagreement on Article 18, i.e. on research on human embryos in vitro.

But the fact that the draft is not yet signed by all European countries does not preclude a future convergence of the respective positions. Indeed there is a need to continue the debate on this topic – not only on a national but also on a supranational level.

In June 2000, the Europäische Akademie Bad Neuenahr-Ahrweiler organised a workshop ”Embryo Experimentation in Europe”. Experts from biology, jurisprudence and philosophy from several different European countries were invited to discuss: current scientific development, moral implications and issues of legislation in new biomedical techniques – taking into account the differences between already existing national legislation and morals.

The papers focussed on three topics: Biological aspects, legal and ethical aspects of cloning and stem cell research, and legal and ethical aspects of PGD.

Biological aspects

To rationally discuss the ethical and legal implications of embryo research, it is essential to ensure that our knowledge of the scientific facts is as complete as possible. The articles of Davor Solter and Robin Lovell-Badge provide an overview of the past, present and likely future of the most interesting and promising recent developments in biology: cloning, using embryonic stem cells for cell and tissue replacement and various other forms of gene therapy. Today cloning is shown to work on many farm and laboratory animals, but there is still a lack of knowledge concerning the reprogramming process and whether the much shorter telomeres of the clones will have negative effects on their health or life span. It is questionable therefore if safety issues will discourage the reproductive cloning of humans in the future. But this might not be the case for therapeutic cloning.

Concerning the use of embryonic stem cells, Davor Solter shows that although there are already some very promising results, several problems will have to be resolved before even a simple cell and tissue replacement therapy using differentiated embryonic stem cells can be implemented. Nevertheless, he expects that conditions for the differentiation of embryonic stem cells into simple tissue will be established quickly and that cells like hematopoietic cells, muscle cells, neurons or even various endocrine cells will soon be available. Because these techniques raise so much controversy, he emphasises that there are also several other multipotential stem cell populations from adult humans which can conceivably be used in cell and tissue replacement beside using embryonic stem cells. But he also shows that the reprogramming of adult cells might not have the same potential as reprogramming embryonic cells.

Robin Lovell-Badge's article complements the previous one by concentrating on the different potential of embryonic and adult stem cells. On the basis of a thorough representation of the new technology for deriving embryonic stem cells, he asks about possible uses of the newly developed nuclear transfer technology for therapeutic purposes and whether it will work well enough to be applied on a patient–specific basis. This would

enable biologists to develop grafts that would not lead to currently typical problems of immune-rejection. Nevertheless, like Solter, Lovell-Badge also warns that biologists have to deal with severe safety risks here.

Legal and Ethical Questions of Cloning and Stem Cell Research

Besides scientific issues we are faced with juridical and, of course, ethical questions. Particularly in questions of embryo experimentation not only moral convictions but also legal regulations differ from country to country – not only between countries with fundamentally different historical and philosophical backgrounds but already within Europe.

Comparing the legislation on research on human embryos of different European states, Deryck Beyleveld and Shaun Pattinson show that it would be too simple to differentiate just between permissive and prohibitive countries. There are many differences not only in the legislation on experiments as such but also in legislation on different closely related topics like the licensing of research, the preservation of human embryos, etc.
Under the given circumstances, Europeans need to decide how to deal with this plurality of legislation. Different opportunities have to be considered: should there be one common regulation for all European countries? And if yes, should it be all permissive or all prohibitive? Should we conclude that harmonisation is neither required nor desirable? Or that there is a need for strategies for non-harmonisation under the given circumstances?

Jacek Hołówka in his article emphasises that every culture is based on certain values that may not be directly perceived, but which are responsible for our collective identity and collective life plans. But what makes some of us sometimes grant an almost even higher protection status to embryos than to infants? And why are many positions on this topic presented and defended almost with a sense of awe? Taking a step back from questions of legal harmonisation Hołówka concentrates on questions of whether it is acceptable to use embryos in order to assist research and therapeutic

purposes. He thereby particularly scrutinises a common difference in attitudes: to distinguish between using spare human embryos from IVF procedures vs. embryos that have been created for the sole purpose of being used in research. Using the theory of Freud he is aiming to draw a line between sound cultural abhorrence and neurotic fears when talking about embryo research, cloning and related issues.

Legal and Ethical Considerations concerning Preimplantation and Prenatal Diagnosis (PGD)

One of the most controversially debated issues in the context of embryo research is the testing of embryos for genetic disorders before implantation in the mother's womb.

As Hans Lilie shows, particularly in Germany legal permission for selection procedures involving human life is discussed against the background of what happened during the Nazi regime. It seems plausible that this experience is one of the main reasons why PGD is not permitted in Germany. Nevertheless, the German law is often accused of being inconsistent: selection of the early embryo via PGD is criticised whereas abortion of the fetus up to the very end of the pregnancy goes unpunished when founded on maternal indication.

Can this distinction between preimplantation and prenatal diagnosis be upheld by moral arguments? Referring to the German Embryo Protection Act, Günther Patzig shows that parts of this law can lead to moral dilemmas that cannot easily be resolved. He criticises underlying misgivings about this legislation, particularly the so-called slippery slope arguments. By many it is feared that the new techniques of diagnosis might lead to a change of attitude in our society towards handicapped people and that persons who live with handicaps caused by genetic disorders might feel insecure concerning their own right to life and/or that a kind of "voluntary coercion" to test all embryos for genetic disorders might occur in the future. How can we deal with these misgivings, and how much weight should we be willing to give to them, he asks.

All articles show that there are still many questions to be dealt with before a well-founded discussion on how to regulate research on and experimentation with human embryos on a European level even can be started properly. Risks and likely benefits of research and experiments have to be clarified. Moral values have to be compared and often even have to be made comparable first of all. Questions of when human life begins and of how much influence moral convictions should be given on legal regulations have to be discussed on a sound scientific and juridical basis without prejudice and as thoroughly as possible.

And last but not least, it has to be discussed how topics like embryo experimentation should be dealt with within the context of the project of harmonisation of the European Union.

This volume of the Grey Series aims at giving a new input to the debate, which in the long run certainly cannot remain within national borders but has to be settled on the European level.

Minou B. Friele

2. EMBRYONIC STEM CELLS AND CLONING:

A new era in human biology and medicine[1]

Davor Solter

ABSTRACT

The cloning of mammals using nuclei donated from adult cells has been achieved and the same procedure can, at least theoretically, be used to clone humans. A parallel technological advance, the derivation of human embryonic stem cells, opens up new possibilities in cell and tissue replacement therapy and heralds significant improvements in gene therapy. Besides potentially valuable medical applications, using these techniques could enrich our understanding of basic mechanisms regulating human development. On the other hand, these preliminary studies are viewed by many as opening Pandora's box and loud voices are clamoring that research in these areas must be forbidden in perpetuity. I suggest in this article that at present we do not know enough to make anything but an emotional decision about the future of these techniques. I try to summarize the current state of the knowledge in the field and indicate how much further research is necessary if benefits and drawbacks are to be properly understood.

INTRODUCTION

Recent technological advances encompassing whole genome sequencing, cloning of mammals using adult cells as nuclear donors and establishment

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[1] This text represents a modified and updated version of the paper originally published in the Croatian Medical Journal (Solter, D: Cloning and Embryonic Stem Cells: a New Era in Human Biology and Medicine), the full text of which can be found on the Internet <http://www.mefst.hr/cmj/1999/4003/400301.htm>. My thanks to CMJ for the permission to reproduce parts of the text. I also thank Dr. Randall Cassada for his valuable editorial help. This paper was written while Davor Solter was a Scholar-in-Residence at the Fogarty International Center for Advanced Study in the Health Sciences, National Institutes of Health, Bethesda, MD, USA.

of human embryonic stem cell lines came so quickly that they outpaced both our biological understanding and our grasp of the ethical, sociological and moral dilemmas involved. It is essential that we try to assess calmly what these technologies do and do not offer, what is necessary to be done if we are to use them wisely and profitably, in essence where we stand and where exactly we wish to go. In the profuse recent writing about these themes single-issue views, be they economical, scientific or ethical, dominate, and balanced approaches seem to have been lost. Here I will try to delineate what we know for sure, how much we can reasonably infer and how much we do not know and will not know without further research. The whole sequence of the human genome will soon be known, and this provides one essential prerequisite for any rational approach toward mapping our future goals. We will need to know the function of the genes and the role they play - or fail to play - singly or in various combinations in causing or contributing to a multitude of human diseases. In designing ways to prevent or alleviate errors in our genetic makeup, various approaches and methods which today we can barely glimpse will have to be developed and understood. Some of these strategies will likely involve cloning and embryonic stem cell technologies, so it is important to understand clearly their potential and use.

CLONING – PAST, PRESENT, FUTURE

Cloning, the derivation of several genetically identical entities from a single individual, has been with us for most of our history. Anybody who has ever taken a twig of a plant and grown a new plant from it was engaged in cloning. The possibility to clone simple animals, vertebrates and finally humans has fascinated many, though it raises numerous important scientific questions. Now large sociological implications have also become obvious. For our purposes we will restrict ourselves to the recent advances in cloning adult mammals, and for background information the reader is referred to the recent book by Di Berardino(1).

Cloning essentially involves replacing all the genetic material or DNA of the egg with the genetic material of a somatic cell from a donor embryo

or adult. Once the technical aspects of the procedure were solved for mammals in the early eighties, numerous attempts to clone various laboratory or farm animals ensued with variable and rather modest success. Embryonic cells were used as nuclear donors, on the logical assumption that the closer the nuclear donor is in developmental terms to the egg, the more successful nuclear transfer is likely to be. Pioneer nuclear transfer experiments done in frogs had suggested that while cloning from embryonic cells may be possible, cloning from adult cells would be considerably harder if not unattainable. This way of thinking persisted until 1996 when the report of cloned sheep derived from an established cell line(2) suggested for the first time that cloning from adult cells may indeed be possible(3), and it was accomplished one year later with the birth of Dolly(4). Rarely has a scientific report caused so much public attention and controversy. The implication that it presaged the cloning of humans released a veritable flood of books, articles and opinions. Where do we stand now, three years later? Dolly was followed by several more sheep, cows(5) and recently mice(6-8). As other farm and laboratory animals are cloned, these are usually first announced in the popular press and not in scientific articles.

The number of cloned mammals is still relatively small, but we can learn something from the available data. First cloning from adult cell nuclei is clearly a very inefficient procedure. Over 400 manipulated embryos resulted in one sheep(4), 250 gave eight calves(5) and about 2500 manipulated embryos developed into 31 newborn mice(6). The results of postnatal development are even more daunting as 4 of the eight calves died soon after birth, as did 9 out of 31 mice. We know very little about what is going on in the somatic nucleus transferred into the enucleated oocyte. It has to undergo reprogramming, a mysterious process whose molecular aspects we can only speculate on. After fertilization the sperm and egg genomes, both at this time transcriptionally silent, are apparently reprogrammed by the cytoplasm so as to activate them for embryonic development. The question is can egg cytoplasm reprogram any other genome besides egg and sperm? Cloning successes indicate that it can, but the low rates suggest that it can do so only very poorly.

When we discuss human cloning and if it should be permitted or forbidden, these data are highly relevant. Some failures in reprogramming might be compatible with development to birth, but the high death rate of newborns (5, 6) or even weeks later(9) indicate delayed consequences. At present we do not know the extent of the necessary reprogramming, how many genes are involved, whether it depends on the kind of cell used as nuclear donor, etc. This looming ignorance is quite sufficient to qualify human cloning for the time being as a medically unsafe and dangerous procedure which certainly should be discouraged until we know more.

What then are the benefits to be derived from the application of cloning technology? This depends to a large extent on who or what is being cloned(7) (Fig. 1). Cloning of laboratory animals, notably mice, will provide us with many important answers to basic biological questions. Our present understanding of the molecular biology of early mammalian development is very limited compared to what is known for lower animals. Several of the genes with important functions during mammalian development are controlled by the process called imprinting. Briefly, the activity of imprinted genes depends on the parent of origin, so that the copy from one parent is active and the other is not(10-12). Imprinting is indispensable for normal development, so some of the somatic cell nuclei used for cloning must have had, i.e. retained, the correct imprint. Are some of the failures of cloning due to the loss of or incorrect imprinting? This seems likely since several imprinted genes are involved in growth control. Examining the ON-OFF status and subsequent expression of imprinted genes following nuclear transfer will significantly help us to understand imprinting and its role in cloning. As we age and our cells divide, the ends of chromosomes – telomeres - become shorter and shorter until they reach a critical length; then the cell dies. This shortening of telomeres may be the basic mechanism of ageing. Presumably the length of telomeres is restored in the germ line. Will nuclear transfer result in telomere repair or will the animals cloned from adult cells start with much shorter telomeres resulting in negative effects on their health or life span? Telomeres of Dolly and a few other cloned sheep were recently found to be abnormally short(13). Is this an additional danger inherent in cloning?

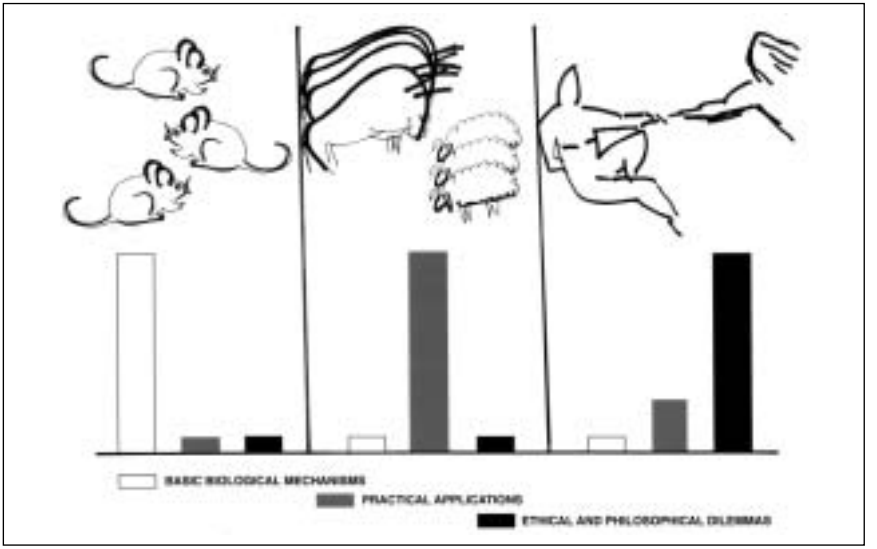

Figure 1.
Emphasis on specific goals to be achieved by cloning depends on the cloned subject. Cloning of laboratory mammals (mostly mice) will be done in order to explore basic biological questions like genome reprogramming, imprinting and X inactivation. The cloning of farm animals will be predominantly done with practical applications in mind so that cloned animals can be used as bioreactors. For this purpose one will have to define a simple but effective cloning procedure which will allow the genetic modification of the nuclear donor cell in culture before it is used for cloning. The cloning of humans may have practical applications, but this possibility has raised numerous ethical and legal questions. Rules regulating the cloning of laboratory and farm animals will be essentially the same as those which currently ensure their safety and humane treatment. Many people believe that the possibility of cloning humans poses an entirely new set of ethical and legal dilemmas.

These sheep are apparently normal so far, but it is too early to tell if they will suffer any future adverse effects.

The cloning of farm animals has always had very practical goals in mind. Numerous attempts to use them as bioreactors began with the advent of transgenesis, i.e. the introduction of extra genes from outside sources. But after injecting DNA into fertilized eggs the yield of transgenic animals was very low and their ability to express the transgene was poor from the beginning or became poor after a few generations. Cloning from genetically modified cells should eliminate most of these problems(14-16).

What about the cloning of humans? At present and for the reasons mentioned above, I think that any such attempt would be irresponsible and in conflict with good medical practice. Safety issues are quite sufficient to discourage the cloning of humans today and there is no real need to invoke any others. But what if we can deal with the biological problems and ensure safety? After all, one might argue, many procedures of assisted reproduction (intracytoplasmic sperm injection, ICSI; injection of egg cytoplasm) have not been properly tested, their safety has certainly not been established, but they are nevertheless used in IVF centers around the world. This situation is unfortunate and, instead of using it to support the permissibility of cloning, the safety of these procedures should be established before we face another possible medically induced tragedy. If in the end we can ensure that cloning is safe or at least not worse than normal reproduction, I see very little reason to forbid it. It is unclear if cloning, despite many opinions to the contrary, raises an entirely new set of moral questions and dilemmas. Viewed as another aspect of ever-increasing reproductive freedom, one is hard pressed to come up with a valid argument to forbid it. We do not prevent reproduction of people who by all biological and sociological standards should not reproduce, it is entirely right that we do not and it is a lasting shame that we once did. Why then forbid somebody to reproduce by cloning? It is likely that the arguments will continue, and at this stage cloning should be forbidden because it is dangerous. If and when it becomes safe, we can hope we will have the collective wisdom to decide if it is right. However, one aspect of cloning, an entirely technical one, nuclear transfer into the enucleated oocyte without subsequent development and birth, may become an essential part of cell therapy of the future, and it is important that this aspect is not confused with cloning leading to reproduction.

EMBRYONIC STEM CELLS – PAST, PRESENT, FUTURE

To understand the potential benefits and limitations of applying embryonic stem cell technologies in human medicine, let us briefly examine this fascinating subject for mouse embryonic stem cells, the best studied case.

Mouse embryonic stem cells (ESCs) were first derived from mouse blastocysts in the early eighties(17, 18); and now we know quite a lot about their biology. Similarly, embryonic germ cells (EGCs) can be derived from primordial germ cells in genital ridges(19-21). Two properties of ESCs have made them especially useful in biological research.

1) ES cells can differentiate *in vitro* and *in vivo*. This ability has always fascinated biologists working with these cells, and its tremendous medical potential is now becoming visible. It is quite clear that differentiation of ES cells in culture can be directed along desired pathways and, combined with some kind of selection, a reasonably pure population of differentiated cells can be isolated(22-25).

b) ES cells can contribute to the germ line in chimeric mice. Soon after their isolation, the totipotency of ES cells was revealed by injecting them into normal blastocysts(26). This means they can contribute to all adult tissues, most importantly as functional germ cells. This, and the newly gained ability to manipulate the genes of ES cells in culture by homologous recombination, has revolutionized mouse genetics. Changing DNA by homologous recombination allows the elimination or alteration of any known gene in hand, and such a mutation can then be bred in whole animals through the germ line derived from ES cells. Thereby its developmental or ”phenotypic” consequences can be analyzed(27-29). Thanks to this, our understanding of how genes function in the organism has advanced dramatically(30). As described below, manipulation of the genome of ES cells will have significant use in future therapeutic modalities, but the imminent medical application of these cells is more predicated on their ability to differentiate.

Human stem cell lines with properties similar to mouse ES cells have recently been isolated from human blastocysts(31), or from human primordial germ cells(32), human EGCs. At this moment the possible uses of human stem cells are all in the future and many complex biological, medical and ethical issues have to be resolved. So this is a good time to consider what the possible applications are and which experiments might be done to make these a reality. We are assuming that human ES cells are

going to be similar in their properties to mouse ES cells, but this is not certain. Although the cell lines derived so far are not optimal, we can envision their use in cell and tissue replacement therapy(33-36). Envision, yes, but quite a number of hurdles remain, so it is crucial that current research on human ES cells not be forbidden for irrelevant reasons before we know for sure if the cells are really useful.

Mouse ES cells can differentiate into many cell types and we now know a great deal about factors and culture conditions which induce differentiation in which direction. Given the many likely ensuing health benefits, similar research with human ESCs should attract more attention and funding, thus enabling it to proceed faster. We can reasonably expect that conditions for differentiation of ESCs into simple tissues will be established quickly and that hematopoietic cells, muscle cells, neurons or even various endocrine cells will soon be available (Fig. 2). Beside differentiation into simple tissues, one can even envision the formation of more complex organs from differentiated ES cells. Using various polymers as scaffolding and colonizing such scaffoldings with endothelial and smooth

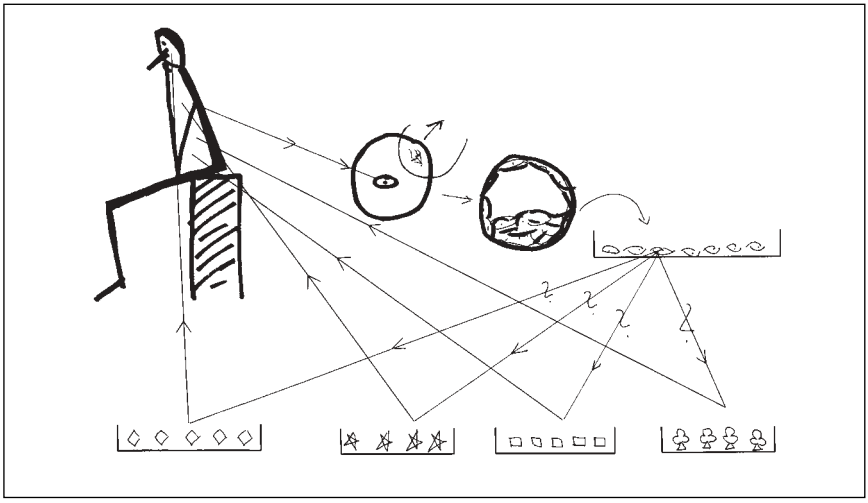

Figure 2. *Possible use of human embryonic stem cells in cell and tissue replacement. An adult cell of a given individual serves as nuclear donor and ES cells are derived from the resulting blastocyst. ES cells are induced to differentiate into various cell types depending on the need and these are implanted back into the original nuclear donor. With such "autologous" cells all problems of allotransplantation are avoided.*

muscle cells, investigators have succeeded in producing *in vitro* functional arteries(37, 38) which were then successfully implanted into pigs. Likewise, a functional urinary bladder was produced from biodegradable polymers formed into bladder shape upon which smooth muscle and urothelial cells were cultured. These bladders were implanted into dogs, replacing their own bladders, and they functioned normally for up to 11 months(39, 40). One could envision that, by recapitulating the normal complex cell and tissue interactions and various extracellular matrices, it may be possible to build complex organs like the kidney in culture - or even a heart.

Embryonic Stem Cells and Gene Therapy

Beside cell and tissue replacement, differentiated ES cell derivatives will likely be used in the future in various forms of gene therapy. At present gene replacement therapy for single gene genetic deficiencies involves risks and works rather poorly for various reasons. It is difficult to have a very efficient and reliable gene delivery system which is at the same time safe. And, once the desired DNA is delivered into the host cells and actually integrates into their genomes, the expression of the transgene is usually poor and short-lived. The most likely cause is that the majority of random integration sites is unsuitable, and the integrated gene is rapidly turned off. Using ES cells, we can target the selected gene to its appropriate place by homologous recombination, thus securing its proper expression. Once the correct integration event has been identified, the cell can be selected. Still an ES cell, it can then be induced to differentiate and the targeted differentiated derivatives introduced into the patient.

Several problems will have to be resolved before even a simple cell and tissue replacement therapy using differentiated ES cells can be implemented. Based on our experience with mouse cells, differentiation along one desired pathway is never complete and several other differentiated cell types are usually present in culture. Vital markers for each desired cell type must be developed so that the sought after cells can be screened for or directly selected for survival(22). Having several differentiated cell types in such a culture would be a nuisance, but the presence of undifferentiated ES cells could be disastrous. ES cells in mice are always tumo-

rigenic when injected, resulting in the growth of teratocarcinomas, so it will thus be essential to eliminate all undifferentiated ES cells prior to cell replacement therapy. We will have to explore extensively in mice what the tumorigenic potential of ES cells is, i.e. if a threshold number of ES cells is required to produce tumors. But mice are very short-lived compared with humans, so they may not be the ideal model to assess the long-term danger of ES cell-based therapy.

The Future

Now we have visualized some of the potential benefits and problems in using ES cells in human medicine. What needs to be done in the near future in order to make their use possible? Intensive work has to be initiated on all aspects of differentiation, determining the necessary culture conditions, identifying promoter factors, differentiation factors and selection markers. Most of this can and will be done using mouse ES cells or human ES cells isolated so far. But the real benefit will be achieved only if the appropriate cell types are derived from the very individual who needs them, i.e. so-called autologous cells (Fig. 2). In the meantime, as is the current practice in organ transplantation, one could resort to life-long immunosuppressive drugs or set up large panels of donor ES cells so that patients can find at least an approximate match. But such allogeneic transplantation has many negative long-term consequences(41) and the continuous use of immunosuppressive drugs may lead to cancer(42, 43). It is one thing to accept something if there is no better alternative, but someday we will likely be able to derive an autologous ES cell line for anybody who needs it. This might be accomplished in three ways and there may be more (Fig. 3). First and most likely to succeed is to take the nucleus from a somatic cell of a given individual and introduce it into an enucleated human egg, let this embryo develop to a blastocyst and derive an ES cell line as described(31). Though there may be technical problems, these are likely to be minimal and the major obstacle to this approach will be of an ethical nature. This procedure is identical to the first stages of cloning and the resulting blastocyst which will be destroyed in order to make the cells is a potential human being. The emphasis is on ”potential”, since the actual likelihood of its development to term, were it to be implanted into

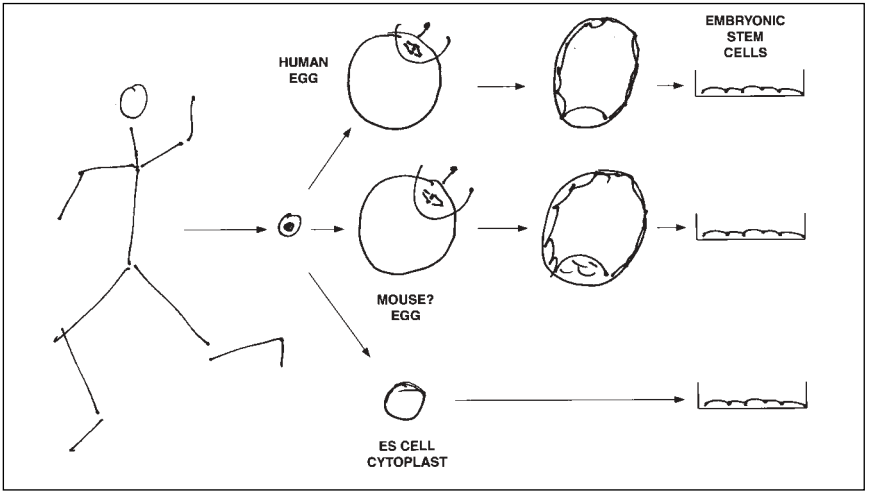

Figure 3. *Three possible ways to make individualized ES cells.*

The nucleus from an adult cell is introduced into 1) a human egg or 2) non-human, mammalian egg or 3) into an ES cell cytoplast (i.e. enucleated ES cell). Each of these procedures could theoretically reprogram the adult nucleus, but the question remains as to which is the most efficient and if all three result in functional ES cells.

the uterus, is very small given the low success rate of cloning. ”Very small” is nevertheless not ”zero” and in countries where the destruction of embryos is not permitted this approach will not be possible. One could argue that the benefit to the health of an adult necessitates the destruction of such embryos, like the argument which supports abortion on medical grounds. However, this embryo would have been made in order to be destroyed and, regardless of the benefits, some individuals and societies may find this unacceptable.

Alternatively one might use a non-human (mouse, cow, sheep) egg as the nuclear donor, and one such attempt was purportedly made and reported in the popular press(44). It is not at all clear how successful this was, and our limited experience with cross-species nuclear transfer has been rather disappointing(45). Even if it works, the nature of the resulting blastocyst is not clear and some may argue that it is also a human embryo with all the problems this entails. The third option, the least controversial but also the least likely to succeed (without further research), is to use an enucleated cell of an existing human ES cell line as the nuclear recipient and hope

that it can reprogram the nucleus of the somatic cell. There is some evidence that partial gene reprogamming can occur in such somatic cell hybrids or cybrids(46). Given the need for autologous ES cell lines and the ethical and legal problems connected with the other approaches, work on this third way will likely intensify.

Human embryonic stem cells have been isolated only recently and nobody really knows if they will be as useful as we would like to think. Nevertheless, their appearance has generated another flurry of mindless publicity, mostly from individuals who are ignorant of the biology involved and who have not taken the time to become informed or to reflect. Endless arguments as to whether ES cells are equivalent to embryos (they are not), and whether one should be allowed to work with them even if one is not allowed to isolate them have highlighted this controversy. Each country seems to be coming up with its own set of near-sighted and hasty decisions. It is refreshing to see that the National Bioethics Advisory Commission to the US President has realized the absurdity of allowing federal funds to be spent for research on ES cells but not on their derivation. Numerous opinions, for and against, some quoted here, can be found in any weekly issue of **Science** or **Nature** and in the popular press(47-54) for anyone concerned.

Since human ES cell technology raises so much controversy, are there any alternatives? Yes. It seems that our bodies contain a large number of various stem cells, more than had been thought till recently. Most of our epithelia are constantly being renewed and stem cells are the basis for this process. There are also several multipotential stem cell populations which can conceivably be used in cell and tissue replacement(55). Neural crest stem cells isolated from fetal peripheral nerve give rise to neurons and glia when transplanted into adults(56, 57). If such cells can also be isolated from adult peripheral nerves, one can easily imagine their application in the therapy of various degenerative diseases of the nervous system.

Neural stem cells derived from adult ependymal cells can differentiate into neurons and astrocytes(58). Interestingly, these stem cells not only repopulate the central nervous system but can also give rise to hemato-

poietic cells which repopulate the bone marrow(59). Although not totipotent, some stem cells may have quite a broad differentiation potential, not restricted to their tissues and organs of origin. Further examples of such multipotential stem cells are human adult mesenchymal stem cells which can differentiate into adipocytes, chondrocytes and osteocytes(60) or bone marrow stem cells which gave rise to hepatic oval cells and were able to colonize the liver after hepatotoxic injury(61). Many needs for cell and tissue replacement therapies could be satisfied by the stem cells present in every adult, and research along these lines should have high priority(62).

Why then bother with human embryonic stem cells? Firstly, some types of organotypic stem cells probably cannot be isolated readily and only derived from ES cells. It could also be argued that derivation of ES cells from a given individual would satisfy all his or her future needs without having to keep isolating different stem cells with restricted potency. Secondly and more importantly, we should consider also the conceivable long-term future applications, some relatively simple and straightforward and some requiring substantial advances. Besides simple cell and tissue therapy, the same cells could be used as vehicles for gene therapy and there are numerous levels on which this could be done. The most logical and, dare one say, ”natural” use can be illustrated by the following example. Different hemoglobinopathies like sickle cell disease or thalassemia are caused by various mutations affecting the structure or synthesis of α and β-globin. Using ES cells derived from an affected individual by one of the methods described above, the affected gene could be replaced by a healthy gene using homologous recombination. The resultant ES cell clone could be induced to differentiate into hematopoietic stem cells, and these then injected back into the same patient to repopulate the bone marrow, so a continuing supply of healthy blood cells would be produced. This would represent a complete and permanent cure of the genetic defect.

We can imagine the further applications, e.g. to help couples with genetic disorders to have normal children without the defect. Most of these applications lie only in the future and some may be difficult or impossible, but there is no obvious biological reason why they should not work. We

should note that if DNA replacement using ES cell technology can correct mutations, putative genetic ”enhancements” by DNA addition will also be possible. At the present time the specter of genetic enhancement is always raised by the critics of this research, although we do not know now what genes to add to improve our genetic heritage. This does not mean that we will never know. One has to bear this in mind and hope that, as our technical abilities and biological knowledge advance, the growth of wisdom to use them wisely and ethically will keep pace.

CONCLUSIONS

The cloning of mammals using adult cells as nuclear donors and the establishment of human embryonic stem cells are two technologies with the potential to revolutionize human medicine and reproduction. Before their potential could be truly assessed, both technologies became mired in numerous relevant and irrelevant moral, ethical and legal controversies. In these discussions it is often ignored that we actually do not know whether all or any of the putative uses will prove to be practical or even possible. Attempts to forbid a priori the use of these technologies will deprive us of both essential biological knowledge and potential beneficial therapeutic modalities. The cloning of humans should be discouraged for now on the grounds of safety, and considerably more research is necessary to establish which aspects determine the outcome of nuclear reprogramming and cloning. The study of human embryonic stem cells is in its infancy and, while many experiments can be done using mouse embryonic stem cells, techniques aimed at practical applications in human medicine must be ultimately established using human cells. We already have clear guidelines regulating tissue and organ transplantation, and work involving human embryonic stem cells can easily be controlled using the same existing regulations. Every country and ultimately all individuals will have to decide for themselves how they feel about the moral aspects of the use of these technologies, but strident demands to forbid them before they are fully understood are short-sighted and probably detrimental. If we are asked to decide to give up something, it seems logical that we should know exactly what it is that we are giving up.

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3. STEM CELL THERAPY: THE POTENTIAL IMPORTANCE OF RESEARCH INTO "THERAPEUTIC CLONING", EMBRYONIC STEM CELLS AND ADULT STEM CELLS.

Robin Lovell-Badge

INTRODUCTION

We have now become very used to the idea of organ transplants in medicine, for a wide range of problems from cataracts to kidney or heart failure. However, we are also all aware of the frequency with which they fail. Immune rejection is one of the most common causes of graft or transplant failure (contaminating pathogens being another major problem). There is also a serious shortage of donors.

What can we do about this ? Both problems could be solved if autologous grafts are performed, taking tissue from one part of the body to repair another. But there are relatively few cases where this can be done at present – skin grafts for burns victims, or valves from leg veins used to repair heart valves.

Rather than using whole organs or tissues, an alternative would be to isolate and use special cells called stem cells. In fact we already do this with skin grafts as mentioned above, or with bone marrow transplants, where the stem cells in the bone marrow can regenerate all the different types of cell in the blood. However, we are all aware how difficult it is to find the correct tissue match to do this. The ideal source being an identical twin, which few of us have. But there are many other types of stem cell. Could these be used for therapy ?

STEM CELLS

First, how do we define a stem cell ? When a mature or differentiated cell divides, it can only give rise to the same type of cell. However, when a stem cell divides, it gives rise to another stem cell (i.e. self renew) and to

a cell that is differentiated. The latter may still be able to divide, but it can not go back to form the original type of cell (see Fig. 1).

There are many different types of stem cell and these are present at all stages from the early embryo to the adult. Stem cells that are present in the embryo, tend to divide frequently, and many have the potential to give rise to a wide range of more specialised cell types. They are therefore considered as multipotent stem cells (Fig. 1).

Adult stem cells are present in many tissues, but they are often quite rare and divide infrequently. They also tend to have limited potential, indeed, stem cells have not been recognised for many cell types in the adult. For example, those that would give rise to the cells of the lung epithelium that are defective in Cystic Fibrosis. Where adult stem cells do occur, they are usually in tune with the organ to which they belong, dividing at the appro-

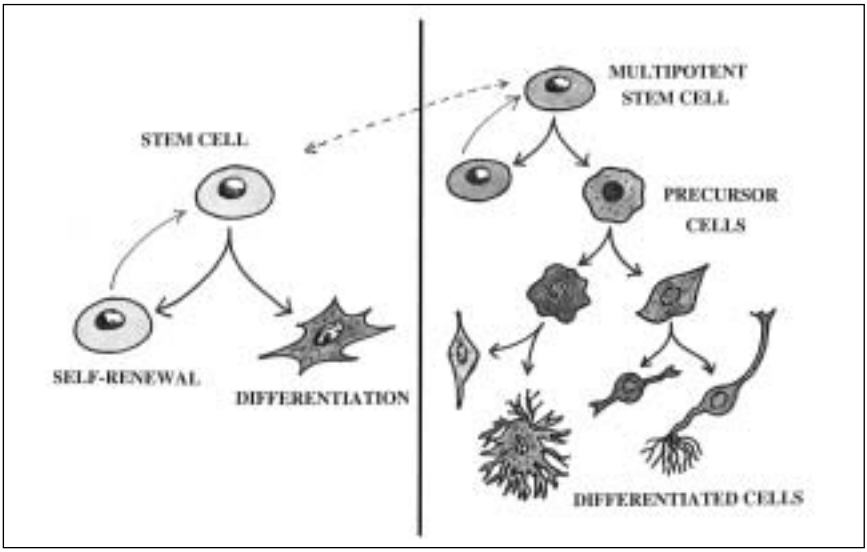

Figure 1.

On the left, when it divides, a typical adult stem cell is shown to give rise to a more mature, or differentiated, cell type as well as a cell similar to the original cell type (self-renewal). On the right, a multipotent stem cell, which is more typical of the embryo, is able to give rise to many types of differentiated cells in addition to self-renewal. The dashed arrow between the two types of stem cell reflects recent evidence that one stem cell type can give rise to another in some circumstances.

priate rate to both self renew and give rise to just sufficient differentiated cell types to replenish those that have been lost. For example, in the blood, skin or brain. However, with accidental trauma or disease the normal rate of regeneration is often too low to allow repair. This is particularly true within the nervous system, but also in other tissues where the normal rate of turnover is low, such as the pancreas.

The idea behind stem cell therapy, is to isolate such cells, multiply them *in vitro* and then use them to replace damaged tissue. This is exactly as is done to repair skin in burns victims. However, many more types of disease could be treated in this way than with conventional organ transplants, as often it is one cell type that has gone wrong rather than the whole organ. It may also be particularly suitable for chronic debilitating diseases, such as Parkinson's, Multiple Sclerosis, diabetes, etc.

However, in many of these diseases, as well as in cases where there is more acute organ failure, it may be too difficult to isolate the appropriate stem cells from the affected tissue in the patient. The stem cells may already be defective, too rare or no longer present at all. Even if they could be isolated, they may not be able to grow well enough *in vitro* to give sufficient numbers of cells for therapy.

Each type of adult stem cell was thought to be able to give rise only to its normal range of mature cell types. However, recent, very exciting work has now suggested that, in some circumstances, it is possible for one type of stem cell to change into another. For example, for a blood stem cell to give nerves. This might allow patient-specific stem cell therapy, where stem cells from one part of the body are used to repair damage to another. I will return to this later.

The stem cells with the greatest potential, however, are the so-called, Embryonic Stem cells. These are derived from an early preimplantation embryo stage called a blastocyst. Figure 2 shows a mouse blastocyst, which corresponds to about 3 days of development post fertilisation. This is similar to a human blastocyst at 5 days of development. At this stage there are a maximum of 100 cells, comprising just two cell types. The outer ones will form part of the placenta (trophoblast), the inner cells

(inner cell mass or ICM) will form the embryo itself, although much later, after implantation. In fact, even though cells of the ICM may each have the potential to contribute to the embryo proper, the majority of them will give rise to other components of the placenta and to membranes such as the amnion, yolk sac, allantois and umbilicus. These all provide the support system for the embryo, but are discarded at birth. In fact, it is not possible to point to a single cell at the blastocyst stage and say that this will contribute to the newborn animal or person. The cells do not know what they will become, therefore we can not possibly know.

Both cell types in the blastocyst depend on each other for their proper development and survival. Thus the inner cells will not develop into an embryo if they are removed from the outer cells. However, they can be grown in a petri dish where, at high frequency, they give rise to Embryonic Stem cells (Fig. 2, centre).

Embryonic Stem cells have a number of remarkable properties. They can essentially be grown indefinitely, and in very large numbers. However, they are not “transformed” like other permanent cell lines. (Transformed means that they have undergone some mutation in a gene that allows permanent growth or they carry a transforming gene from a virus or tumour

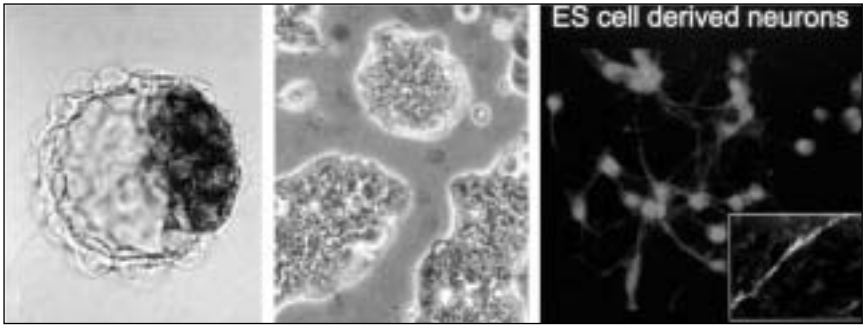

Figure 2.

Left panel: A mouse blastocyst at 3.5 days of development. Cells of the inner cell mass are revealed with a dark stain. Centre panel: Mouse Embryonic Stem cells. Right panel: A pure population of neurons derived entirely in vitro from differentiating Embryonic Stem cells. The inset shows such a neuron after transplantation into a newborn mouse brain (data from Austin Smith).

that has the same effect.) Embryonic Stem cells are normal cells by all criteria, such as their chromosome make up (karyotype). They also have the ability, under the right conditions, to give rise to all cell types of the body. The best test of this in the mouse is to inject them into a blastocyst, where they reintegrate into the ICM and can contribute to all tissues in the resulting chimaera. Such chimaeric mice can live a normal life, with no greater incidence of tumours, etc. than found in the strains of mice used to make them.

However, Embryonic Stem cells can also form a wide range of cell types *in vitro*. We already know how to direct them to form certain types of cell purely in culture (see Fig. 2, right panel). For example, nerve cells, muscle cells, cells that form blood vessels, pancreatic islet cells. Cells made like this can then be grafted back into animals, where they have been shown to at least partially correct a range of diseases. These include mouse models of Parkinson's Disease, myelin-deficient (md) rats (a good animal model for the hereditary human myelin disorder Pelizaeus-Merzbacher disease, which has some relevance to multiple sclerosis) and diabetes. (See further discussion below and Table 1.)

We have been studying Embryonic Stem (ES) cells in the mouse for a long time, at least 20 years, so we know a lot about them. But since the work of Jamie Thompson and his colleagues two years ago, we now know it is possible to make them from human blastocyst stage embryos as well. They clearly share many of the properties possessed by mouse ES cells, including the ability to make many different cell types in culture.

So, could we use human ES cell lines to treat any of a wide range of diseases, by cell-based therapies ? It would seem likely, except for the big problem of immune rejection. The few lines that have been established so far (in other countries), would not overcome this problem. One possibility is to have available many lines, perhaps a bank of 100 or even 1000 or so, which would be tissue-typed, so that a close enough match would be available for most patients and for most types of therapy. This would still require the use of immunosuppressive drugs to prevent rejection of grafted cells, which can have a number of more or less severe conse-

quences to the patient, including increased likelihood of infections or (possibly) tumours. These consequences would have to be weighed against the likely benefit of the therapy. Some types of graft are known to require closer tissue matches than others – bone marrow grafts being the most extreme case (partly because there is the possibility that the graft can reject the host, as well as the usual problem of the host rejecting the graft). However, other potential cell-based therapies may also require very close tissue-matching. For example, many cases of diabetes occur when the β-cells in the islets of the pancreas, which are the cells that make insulin, have been destroyed by the patients own immune system.

The ideal option would be to isolate Embryonic Stem cells from the patient, but of course the right cell type to do this only exists within the very early embryo. What if we could reverse the normal direction of differentiation and obtain suitable stem cells from an adult cell ? The nuclear transfer (cloning) techniques, that gave rise to Dolly and subsequently to cloned mice, cows, goats and pigs, showed that it is indeed possible to reprogramme the nucleus of an adult cell.

CELL-NUCLEAR REPLACEMENT OR "THERAPEUTIC CLONING"

The rationale behind these experiments was that the most likely source of a factor that could reprogramme an adult cell to become an embryo cell, would be from an early embryo itself or from the cells that normally have the potential to give rise to an embryo. These are the germ cells, which are present as unfertilised eggs in the female and as sperm in the male. It is a great pity, but we can not use sperm to reprogramme. They are present in vast numbers, but they are useless. Some would argue that they are typically male ! As usual, we have to turn to women to provide the solution.

The unfertilised egg (or oocyte), which, apart from carrying one set of chromosomes containing the genetic information in DNA, has a large amount of cytoplasm. This contains the factors that normally reprogramme the incoming sperm nucleus into one appropriate for an early embryo (Fig. 3). It also turns out that this cytoplasm can reprogramme an adult

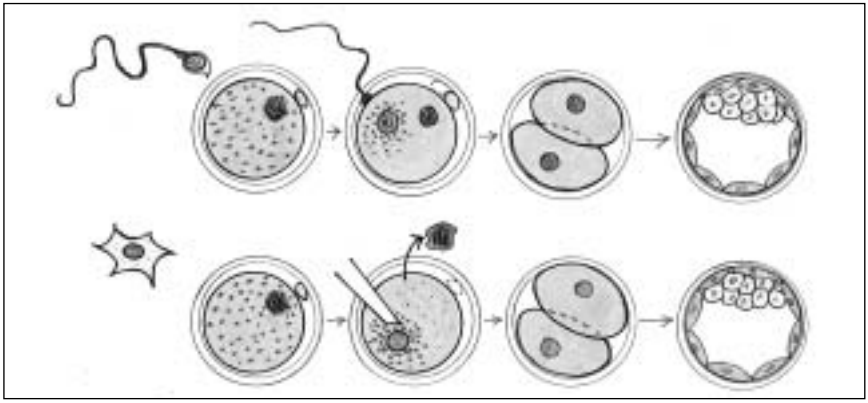

Figure 3.

The sequence at top shows normal fertilisation of an egg and its development to a blastocyst stage early embryo. The hypothetical factor(s) responsible for reprogramming the incoming sperm nucleus are indicated as darker dots.The sequence below shows the nuclear transfer procedure to remove the genetic material from the unfertilised egg and to reprogramme an adult cell nucleus, and subsequent development in culture to a blastocyst, from which ES cells could be derived.

cell nucleus, essentially tricking it into "thinking" that it is the nucleus of a one-cell embryo. So, by removing the oocyte's own nucleus and replacing it with that of an adult donor cell, it is possible to obtain an embryo. This is the nuclear transfer technology that allows cloning. Many experiments have shown that an early embryo cell has already lost the ability to reprogramme a transferred nucleus, suggesting that the relevant factors are no longer present once embryonic development is initiated.

It should be absolutely clear, however, that we are not talking about reproductive cloning. This would require that the preimplantation embryo was allowed to develop in the womb (uterus) of a surrogate mother, something that is illegal. It is very easy to draw a strong bright line between development in culture to the blastocyst stage and subsequent development within the uterus. The latter requires so many additional hurdles to be overcome that it is likely to very impractical and it would certainly be very hard to break the law. (In the UK it would require the consent of the egg donor, the clinicians and embryologists willing to perform the procedures, the consent of the surrogate mother (or probably many) and a licence from the HFEA. The latter have made their position on this very clear: they

would not approve it.) Instead, we need to focus on the topic we are debating, namely, can we use this nuclear transfer technology to derive human Embryonic Stem cells that can be used for therapeutic purposes ? And, could it work well enough to be done on a patient–specific basis, to overcome problems of immune-rejection ? The simple answer is we do not know and this is one of the reasons why research in this area is necessary. While the nuclear transfer techniques have worked in a handful of very different species, there are others for which it has so far been unsuccessful (e.g. rats, rabbits and monkeys). We do not know the situation for humans.

PATIENT-SPECIFIC STEM CELL THERAPY

We should consider again the two potential ways of obtaining suitable stem cells for cell-based therapies. These are illustrated in Fig. 4 for the ideal case of patient-specific stem cell therapy, but mostly apply also to the establishment of banks of stem cells from a suitably large and diverse range of individuals or early embryos left over from IVF programmes.

The idea of therapeutic cloning or cell-nuclear replacement technology is shown on the right hand side of Fig. 4. A biopsy would be taken from the patient and by nuclear transfer, reprogramme an adult cell into an early embryo. This would be cultured *in vitro* to the blastocyst stage and then the inner cells isolated and used to derive Embryonic Stem cells. These would have the same genetic make-up as the patient. Indeed, they can be considered an extension of the patient. We could then apply techniques, many of which we have learned from studying mouse Embryonic Stem cells, to direct these to form the relevant cell type to cure the patient, be it Parkinson's, heart disease or spinal cord injury. Indeed, recent work has already suggested that it is possible to direct human ES cells to differentiate along specific pathways. If there is a genetic cause to the disease, such as cystic fibrosis or muscular dystrophy, it may be possible to correct the genetic defect in the stem cells, prior to grafting the cells back into the patient. Techniques for doing this are well established with mouse ES cells. Clearly, once Embryonic Stem cells have been made for an individual, they would be available for treating any other problem present in that person.

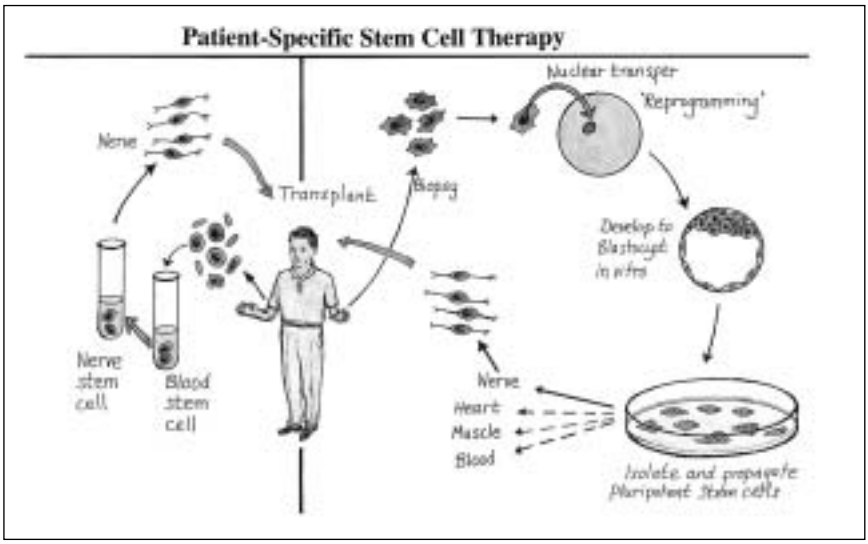

Figure 4.
Patient-specific stem cell therapy. See text for details.

We do not know the best source of cells for the original biopsy. Several cells types have worked in other species, including the tip of the tail in mice, which is essentially a skin biopsy. But this is another area where research is needed. It is possible that some easily accessible human cell types make particularly good nuclear donor cells.

The second way we might be able to obtain a wider range of stem cells for therapy is by redirecting one type of adult stem cell into another. This is illustrated on the left of Fig. 4. In this case, one type of stem cell would be isolated and then reprogrammed into another type of stem cell, appropriate for curing the disease. For example, blood stem cells could be turned into nerve stem cells and then into the appropriate nerves for e.g. curing Parkinson's.

> So, one might ask, if we can do this, then why would we need to even think of using the first method ? I think this is best illustrated by looking at some of the factors that we need to consider before we can attempt to do stem cell therapy, and to compare and contrast the two methods.

REQUIREMENTS FOR STEM CELL THERAPY	
ACCESSIBILITY OF CELLS	– SOURCE
	– RARITY
PROPERTIES IN VITRO	– PURIFICATION
	– GROWTH RATE
	– EASE OF MANIPULATION
	– RANGE OF CELL TYPES
FOR TRANSPLANT	– SAFETY
	– PURITY
	– DESIRED PROPERTIES
AFTER GRAFTING	– SURVIVAL
	– LIFESPAN
	– MAINTAIN FUNCTION

Table 1 lists some of the requirements for stem cell therapy.

1 ACCESSIBILITY.

Adult stem cells are often very rare and inaccessible. Blood stem cells are present at very low numbers in blood (about 1 in 10,000,000). They are more frequent in bone marrow, but still rare, and bone marrow biopsy is an operation with some risk and discomfort. Cord blood, obtained from the umbilicus at birth is another source of blood (hematopoietic) stem cells. These need to be banked and stored in anticipation of any disease. Although this is already being done in some centres, it obviously can not be done retrospectively. Furthermore, in over 1500 publications involving the study or use of cord blood stem cells, so far no paper describes their purification, and there is no indication that they can give rise to any cells other than those typical of the haematopoeitic system. The stem cells of the pancreas, which can give islet cells, are thought to be in the pancreatic ducts, but methods of isolating them so that they can be expanded *in vitro* have not been found. Grafts of islets have been shown to work, but for each patient there is a requirement for multiple

donors and aggressive immunosuppression. With respect to neurons and glia, stem cells do exist in the brain and spinal cord, but these central nervous system or CNS stem cells are rare and tend to be in regions that are difficult to access safely (see Fig. 5). Clearly one would not want to damage CNS tissue getting them out. There is also concern about grafting CNS material from one individual to another, not only because of the possibility of rejection, but also because of hidden diseases such as CJD.

For many adult cell types we do not know where the stem cells are or if they even exist. For example, no one has identified stem cells that would replace the cells that line the lung, needed in cases of Cystic Fibrosis, emphysema or after inhalation burns. On the other hand, we know that Embryonic Stem cells are able to give rise to all cells of the lung in chimaeric mice, so it is likely that they would do so *in vitro*. With an appropriate marker it may be possible to select them and indeed to discover the

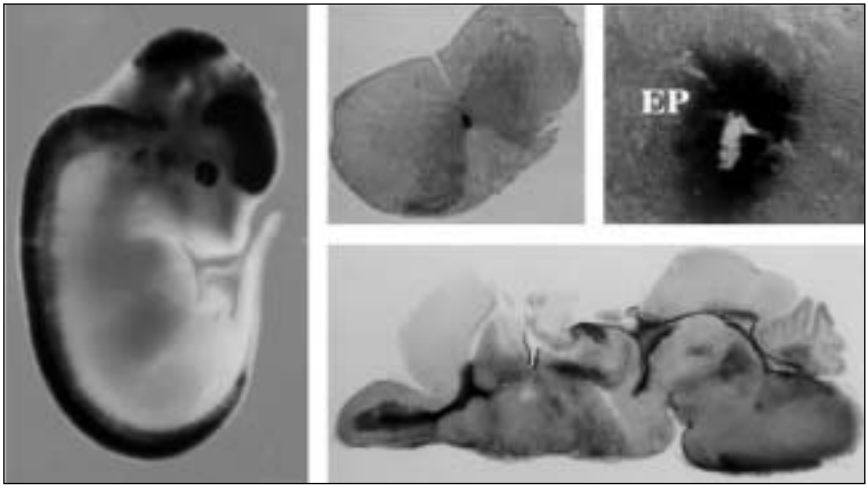

Figure 5.

The panel on the left shows a mouse embryo at about 14 days of development. The blue (here: dark) stain (which detects the activity of a gene called Sox2) reveals much of the central nervous system. Many of the stained cells correspond to embryonic CNS stem cells. The panels to the right, show adult spinal cord (top) and brain. The blue stain (also detecting Sox2 activity), reveals the regions in which adult CNS stem cells are to be found.

cellular pathway that leads to their formation. Such research may allow adult lung stem cells to be found.

To make human Embryonic Stem cells, we need to consider either the use of spare embryos from IVF programmes or the use of nuclear transfer to reprogramme an adult cell. Clearly the number of spare embryos is limiting. However, many more are currently discarded than would be needed to establish say 1000 ES cell lines over a period of a few years. Even from the few studies done so far, it seems that the frequency of deriving human ES cells from normal blastocysts is very high (25-33%). Indeed it may even be better than with mice, where it very strain dependent – as high as 80% with one particular strain (129SV/EV), but down to almost zero with most others. (N.B. There have been no apparent genetic background effects so far in deriving human ES cells: the frequencies were similar with blastocysts obtained in North America and in Singapore. With more experience it may be possible to improve the efficiency of this step even more, but it already seems to be one that is not worth worrying about too much.)

For some people, who believe that life begins at fertilisation, the use of spare embryos left over from IVF programmes to derive Embryonic Stem cell lines would be unacceptable. However, the cell nuclear replacement technique ("therapeutic cloning"), uses unfertilised eggs. These do not have the same moral value and, especially as their genetic material is removed and replaced with an adult cell nucleus, they could be considered just as an extension of the adult: a universal organ available specifically for donation ! If made on a patient-specific basis, this would even overcome some religious objections to transplants between individuals, as the graft would essentially be autologous.

With respect to the use of nuclear transfer to reprogramme an adult cell we need to consider both the source of unfertilised eggs and suitable donor cell type. With respect to the former, some people have raised the problem that there would be a shortage of unfertilised eggs to contemplate anything on a large enough scale to have patient-specific stem cell therapy. This is essentially true if it is necessary to use only those leftover

from IVF programmes. However, it is possible that only a small fraction of egg cytoplasm is required to reprogramme some adult cells. Ultimately, it may be possible to define and isolate the factors from the egg cytoplasm that are responsible. This is one intention of the research that needs to be done. If successful, this would obviate the need to use any eggs.

It is worth mentioning sources of unfertilised eggs other than those available from IVF programmes. Techniques are being developed in the mouse and in farm animals, such as cattle, to remove from the ovary so called primordial follicles, which contain an oocyte that has not yet begun to grow. These are found at all stages from the foetus to the adult. These follicles can then be maintained in culture in conditions that promote growth of the oocyte. In one study in the mouse, such a follicle was isolated from a newborn female mouse, the oocyte grown and matured *in vitro* and then fertilised, also in vitro, to obtain an early embryo, which after embryo transfer, gave rise to a normal liveborn mouse. Ethical issues notwithstanding, this raises the possibility of using oocytes derived from the ovaries of aborted fetuses. (This is currently not permitted in the UK.) We also have to consider that in the future women may become more willing to donate unfertilised eggs. To be blunt, some 100,000,000 unfertilised eggs are flushed down the toilet each year in the UK. Of course it would be difficult to retrieve these (again it is a pity that we can not use sperm). But, one should consider how many women would be willing to undergo the superovulation procedures and surgery necessary to provide a sufficient number of unfertilised eggs, if they know that a loved one could benefit from stem cell therapy ? Clearly it would be unethical to put any pressure on a woman to do so – and as a man I have to be careful even putting this idea forward, but it is something that needs to be considered.

With respect to donor cell types, if a skin biopsy can be used, then this would pose no problems in terms of either source or rarity. If other cell types are found to be even better, and one possibility is that adult stem cells may be easier to reprogramme than differentiated cells, then there is still the advantage that very few cells are actually needed for the nuclear transfer step. We know that skin stem cells are one of the few adult stem cell types able to divide extensively, so perhaps these would be ideal

nucleus donors. However, they have a limited potential. Blood stem cells may be better, if there are simple, robust methods for their isolation.

2 PROPERTIES IN VITRO

It is often difficult to isolate pure populations of stem cells from adult tissues, they tend to grow poorly and they often have a limited lifespan. All cells age as we grow older and stem cells are no exception. This will include a shortening of telomeres, the special regions at the end of chromosomes required to maintain their integrity. Cellular ageing has been associated with telomere shortening. It will also include the accumulation of mutations (see below). Conditions for growing adult stem cells *in vitro* have not been established for most stem cell types: CNS and skin being perhaps the two most notable exceptions. Because the stem cells grow slowly and for a limited number of divisions it may be difficult to obtain sufficient numbers for therapy. One possible way to circumvent this problem is to "transform" them with an "immortalising" viral or cellular oncogene (tumour causing gene). This has been used for some studies in the mouse using adult CNS stem cells (see papers by Evan Snyder) and liver (Kobayashi et al, 2000). However, for use in humans there would have to be robust methods for eliminating the oncogene prior to grafting.

Cells that grow slowly tend to be much harder to manipulate or from which to select desired properties. Indeed, somatic mutation occurring *in vitro* may result in faster growing cells, which will take over the culture. These may have changed in other properties, such that they will no longer be suitable for therapy and indeed they may no longer be safe to use (see below).

With respect to the range of cell types that a given adult stem cell can give rise to, some examples are presented in Table 2. Clearly they can all give rise to the specialised cells that reflect their normal function *in vivo*, i.e. if they had been left in the organ to which they belong. CNS stem cells can therefore give rise to both nerves (neurons) and to several types of support cell, collectively called glial cells. Within the CNS there are several

types of glia, including oligodendrocytes and astrocytes. Schwann cells are the glia of the peripheral nervous system. These may have specific characteristics depending on the neurons with which they interact and the particular region of the nervous system where they are located. With respect to neurons, however, there is a large, very diverse range of cell types. In many of the experiments that have been done so far using adult CNS stem cells, the precise identity of the neurons has not been ascertained. Indeed, some evidence suggests that stem cells isolated from one part of the CNS may only be able to give rise to neurons typical of that region of the CNS. If we have to be even more precise about the source from which

Potential of Adult Stem Cells

Source	Cell Types	Method
Brain	Nerves and Glia	Injection
Brain	Blood	Injection into irradiated mice
Brain	Muscle	Injection to muscle
Brain	Many	Injection into blastocysts
		Co-culture with ES cells
Bone marrow	Blood	Grafting/Injection
Bone marrow	Hepatocytes	Grafting/Injection
Bone Marrow	Heart/skeletal muscle	Injection to muscle
Bone Marrow	Brain Nerves/Glia	Injection in blood system (after irradiation to eliminate host stem cells)
Muscle satellite cells	Muscle	Injection
Muscle	Blood	Injection into irradiated mice
Optic nerve	Neural stem cells	In vitro treatment (02A precursors)

Table 2

they are obtained, this raises further difficulties that will have to be overcome before we can contemplate using adult stem cells for therapy.

Data that has accumulated over the last few years has shown that adult stem cells can give rise to a much greater range of differentiated cell types than expected, even those typical of other tissues. For example, CNS stem cells have been shown to give muscle and blood cell types, while blood (haematopoietic) stem cells can give muscle and liver cells (hepatocytes) and to cells of the CNS (Alison, et al. 2000; . This latter result was described in two recent papers. Adult mouse bone marrow (blood) stem cells when injected into mice that have been irradiated to kill their own blood stem cells or carried a mutation that did so, were able to change their normal fate and give rise to neurons in the injected mice (Brazelton, et al, 2000; Mezey, et al., 2000).

All these results are very exciting from a fundamental scientific point of view and would seem to provide a very useful alternative way to carry out patient-specific stem cell therapy (as outlined in Fig. 4). However, in reality we know almost nothing about the process that allows one adult stem cell type to change into another. We do not know what is responsible for the reprogramming, nor, with a few exceptions, do we how to direct the stem cells to change into any other particular cell type *in vitro*. Moreover, the change of potential occurs very infrequently and is likely to occur with only a few relatively rare cells amongst the original stem cell population. Are these cells normal and safe ?

Apart from a few special cases, the only situations where this change in adult stem cell fate has been seen so far are when the isolated stem cells have been put back into an animal (or human). There is, therefore, essentially no control over the process. For example, with the recent papers mentioned above, the new neuronal material was of several types, including many fairly unspecialised cells, and there was no evidence that the cells were normal or functional. There can not be any control over the type of neuron produced as they have differentiated *in vivo*. Moreover, the bone marrow stem cells may only have colonised the CNS because stem cells in this tissue were also destroyed by the irradiation. This would

explain contributions to the olfactory system where cell renewal is a normal continuous process. (See the commentary that accompanied these two papers by Vogel, (2000)).

In fact the best example which shows that stem cells from the adult mouse brain can give rise to many other mature cell types, came from studies by a Swedish research group (Clarke et al, 2000), where they could reprogramme the cells by injecting them into blastocyst stage mouse embryos. The resulting embryo chimaeras showed contributions from the stem cells in several tissues including muscle, bone, gut, etc, (although apparently not all cell types could be formed). From a fundamental biological research perspective this was a fascinating result. But, clearly we can not and would not want to use this method of reprogramming human stem cells. It was also a rare event, working in only 1% of attempts. This is in contrast to carrying out the same procedure with ES cells, where essentially 100 % of cells (even single cells) injected into a blastocyst can contribute to many tissues in the resulting chimaera. The authors also described a second method, namely to co-culture the CNS stem cells with differentiating ES cells, but there is so far no understanding of how this worked and relatively little control over the process. Unless the factors responsible can be found, one might as well just use the ES cells.

In contrast, Embryonic Stem cells can be purified very easily, they grow very well in culture and they are essentially immortal without the need for "transformation". There is good evidence that the reprogramming by the cell-nuclear replacement ("cloning") technique also rejuvenates the adult cell nucleus. Although the first studies on Dolly indicated that her telomeres are the same length expected for a 6 year old sheep, studies on cloned mice and cattle are different and reveal that the telomeres are restored to the normal expected length.

We know that Embryonic Stem cells can give rise to any cell type within the body, so potentially they can be used to treat any disease. This also applies to the problem of regional specification as discussed above for adult stem cells: ES cells can give rise to any of the many types of neuron found in any part of the nervous system. In addition, we already know

how to select particular cell types from differentiating mouse ES cells and to do this in a controlled manner. There are now many examples, so I list only some, with obvious therapeutic benefits, in Table 3. Most of these have been tested to some extent in animal models of the corresponding human disease or injury. Two recent studies are particularly noteworthy. Firstly, the derivation of a stem cell type able to give rise to all the cell types that make up blood vessels (Yamashita et al, 2000). These would have obvious potential to treat a range of chronic problems, including coronary heart disease. Secondly, through the discovery of a new factor a Japanese team led by Yoshiki Sasai have been able to obtain relatively pure populations of dopaminergic neurons, the cell type that is defective or missing in Parkinson's disease, from ES cells in essentially a one step procedure (Kawasaki et al, 2000). In previous work others have been able to obtain such neurons from ES cells, but only by following a complex

Specific cell types isolated from mouse ES cells

Cell type	Potential for therapy
Cardiac muscle	Heart disease
Skeletal muscle	Muscular dystrophy
Blood vessel progenitors	Coronary and other vascular problems
Haematopoietic cells	Diseases of blood and immune systems To replace HSC after irradiation.
Insulin-secreting	Diabetes
Neural stem cells	Many diseases and accidental trauma
Glial cells	Multiple Sclerosis
Neurons	Alzheimers
Dopaminergic Neurons	Parkinson's

Table 3

method and they comprised only a small fraction of the resulting neuronal cell types. Cells produced by this new method were grafted into the brains of mice that had been chemically depleted of their own dopaminergic neurons, and the grafted cells were shown to produce dopamine. This is clearly a very promising result with respect to potential treatments of Parkinson's disease by cell-based therapies.

3 *REQUIREMENTS FOR TRANSPLANT*

It is obviously very important to know that any cells used for transplant are safe, free from contamination (pathogens and other cell types) and that they have the desired properties. For Embryonic Stem cells, it is normal for them to give rise to many cell types. They follow a similar progression as found in an embryo. However, for an adult stem cell to change its fate it has to undergo an abnormal process. Indeed, in all cases described so far this has been a very inefficient process. Because the ability to change potential is rare, the cells that are able to do so may in fact be abnormal cells. Tumour cells often have the properties of immature cell types and it is likely that many cancers arise from stem cells that have undergone some mutation. As mentioned above, cells tend to accumulate mutations as they age. Clearly we would not want to risk using cells that might lead to cancer.

If using ES cells it is important to be able to remove any undifferentiated ES cells from the cells required for therapy, otherwise they can form a type of tumour called a teratocarcinoma. However, once they have even begun to develop into a more mature cell type they are known to be very safe. It is also important to transplant back only the desired cell types as others may create scar tissue. Several ways of doing this have been established with mouse ES cells, where the wrong cell type can be eliminated and/or the right cell types selected or purified from a mixed population of cells (e.g. Li et al, 1999; Kawasaki et al, 2000). Again, this is an area where research on human ES cells needs to be carried out.

4 *AFTER GRAFTING*

A large number of studies have been conducted (mostly in mice) with grafts of cells derived from differentiating ES cells and some from adult stem cells. It is difficult to review all of these here. However, the results from studies beginning with ES cells have been very promising, frequently demonstrating good survival of the grafted cells and long term maintenance of function. Moreover many cases have shown at least partial rescue of the disease model.

With adult stem cells, some studies show promising results when they are used to replenish the cell type to which they would normally give rise. However, there is little evidence from any of the studies that have been done so far that involve a change of one stem cell type to another, to suggest that this may be either a useful or a safe therapeutic approach.

Perhaps this just means that we need to do much more research, particularly with adult stem cells. Indeed it is likely that results obtained with ES cells can be applied to adult stem cells and vice-versa. But from all the criteria above, it seems that therapeutic approaches arising from ES cells are likely to lead to successful cures for a far greater range of affected tissue types and far sooner than will be possible with adult stem cells.

HOW NEAR ARE WE TO ESTABLISHING METHODS FOR PATIENT-SPECIFIC STEM CELL THERAPY AND WHY DO WE NEED TO DO RESEARCH ON HUMAN EMBRYOS ?

Many of these points have been covered already, but it is worth repeating some of them. Clearly much work can and will be done using animals such as the mouse. Indeed, two recent papers, one published (Munsie et al, 2000) and one in Press (Roger Pederson, personal communication), have shown that it is feasible to begin with a biopsy, carry out nuclear replacement into an unfertilised egg, grow embryos to blastocyst stages in culture and then use these to derive Embryonic Stem cell lines. At least some of the latter were shown to have properties expected of ES cells in terms of their ability to differentiate into a wide range of cell types *in vitro* and in chimaeras.

However, there are many species-specific differences in early development, for example, the rate of development. Furthermore, it is likely that we will need to use human material to reprogramme human cells, especially if they need to follow the normal steps of embryonic development up to the blastocyst stage. This is one reason why it might not be possible to use unfertilised eggs from non-human species. (There are also potential problems about incompatibility between genes in the nucleus and those in the mitochondria in the cytoplasm of the egg.)

We know it is possible at high efficiency to derive Embryonic Stem cells from human blastocysts cultured in vitro from spare embryos obtained in IVF programmes. However, we do not yet know if it is possible to use the nuclear transfer technology to reprogramme adult cells taken from a patient and to obtain suitable blastocyst stage embryos. Nor do we know the best type of cell to use as a nucleus donor. We also need to do research on the best ways to treat any ES cell lines such that we could obtain the right cell type to use for therapy,

It may be that most adult stem cells will be inappropriate and that we need to begin with Embryonic Stem cells to obtain anything useful for cell-based therapies. Promising results from mouse studies have already indicated that cells derived from ES cells in culture can be used to treat a variety of syndromes, such as mouse models of Parkinsons' Disease and diabetes. Do we really want to ignore what seems a very promising method of treating many debilitating diseases ?

We therefore need to begin to explore the usefulness of human ES cells, and as part of this, we need to have methods of quality control to know that any cells used will be safe and reliable. All the evidence obtained with mouse ES cells suggests that they probably will be, but it is important to show this for human ES cells.

We know that Embryonic Stem cells are able to give rise to any cell type within the body. This is a normal process, not one that involves a rare cell changing its potential. They would then seem to be an ideal source of cells for cell-based therapies. However, if they were to be made on a patient-specific basis using current nuclear transfer technology, then this would

require the use of many unfertilised eggs, much more than could be reasonably expected to be left over as spare eggs from IVF. However, the reprogramming mechanism elicited by egg cytoplasm after nuclear transfer, is still the only way we know how to reprogram an adult cell in a controlled manner. We need to be able to define the factors that are responsible and work out how to use them or the technology in a more efficient manner. Once we understand the mechanisms, perhaps we could treat adult cells in an appropriate way to directly turn them into the equivalent of Embryonic Stem cells, eventually without having to use any human eggs.

We are dealing with a question of potential risk versus likely benefits. My personal view is that the benefits are definitely worth pursuing. Moreover, it is better that this type of work is permitted in the context of a well regulated and controlled system, such as that already in place in the UK, where the science can proceed in step with ethical issues, rather than in many countries around the world that have little or no regulation.

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4. Embryo Research in the UK: Is Harmonisation in the EU Needed or Possible?

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ABSTRACT

This paper summarises UK legislation on embryo research and contrasts it with the regulatory position in other countries, particularly those with legislation.

It is argued that moral, social, and economic factors and pressures render non-harmonisation the optimal situation in relation to the interests (broadly conceived) of both those countries that currently prohibit research on embryos and those that permit it. Nevertheless, it is suggested that harmonisation that permits embryo research is likely to be the regulatory outcome in all the EU countries in the medium or long-term.

INTRODUCTION[2]

The regulation of embryo research in the EU differs from country to country. Some countries prohibit it altogether, whereas other permit it to varying degrees. Permission, in particular, may be by legal means or essentially by default. Because prohibition, especially, is driven mainly by moral and religious considerations, there are obvious reasons why prohibition countries would desire prohibition to be EU-wide. At the same time, at least in prohibition countries, scientists who have an interest in embryo research will desire permission to be universal.

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[2] The legal information in this paper has, where possible, been updated and corrected from Beyleveld and Pattinson 2000, which provides a comparative analysis not restricted to embryo research of regulatory mechanisms in the EU addressing genetic and reproductive technologies.
For analysis of the use of the law of tort to regulate embryo research and other genetic or reproductive technologies, see Pattinson 1999.

Of the permissive countries, the UK is generally viewed as the most liberal, and it is the contrast between its position and that of prohibition countries such as Ireland, Germany and Austria that most sharply reveals the gulf that would have to be closed if harmonisation were to be achieved.

We will see that this is an oversimplification, in that there are respects in which the UK is not the most liberal. But, because the UK has the most developed system of regulation, we will begin by detailing its legislative position and contrasting it with other countries, particularly those with legislation.

We will argue that non-harmonisation is nationally optimal (i.e., best serves the different interests a country has) for both countries that currently prohibit research on embryos and countries that permit it. Nonetheless, we will suggest that permitting embryo research is likely to be the regulatory outcome in all the EU countries in the medium or long-term.

It is important that we clarify two matters before we begin. First, we will be concerned with *in vitro* research only. Secondly, we do not consider experimental manipulations to be research if they *must* have as a purpose the direct benefit of the embryo. If we were to consider this research, then Germany, and Austria would have to be considered permissive countries, whereas we consider them to be prohibition countries.

UK REGULATION OF EMBRYO RESEARCH

The UK permits embryo research, which falls under specific legislation—the Human Fertilisation and Embryology Act 1990.

Much of the Act turns on its definition of an embryo, because it regulates the use, storage and creation of embryos outside the body.[3] An embryo is defined as ”an egg in the process of fertilisation”[4] or ”a live

[3] s.3(1) and ss.1(2)&(3). The Act also governs the storage or donation of gametes: s.4(1).
[4] s.1(1)(b).

human embryo where fertilisation is complete",[5] completion being at "the appearance of a two cell zygote".

Both surplus embryos (those produced for assisted reproduction by IVF, but not used for this purpose) and specially created embryos may be used for research.[6]

Research may be carried out on embryos if this is "necessary or desirable" to improve the treatment of infertility, increase knowledge of the causes of congenital disease or of miscarriage, develop more effective contraceptive methods, or to develop methods for detecting gene or chromosome abnormalities of embryos before implantation.[7]

These purposes may be extended by regulation.[8] The Human Genetics Advisory Commission (HGAC) and the Human Fertilisation and Embryology Authority (HFEA) have jointly recommended that research for two additional purposes be permitted—"developing methods of therapy for mitochondrial diseases [and] developing methods of therapy for diseased or damaged tissues or organs."[9] The latter would authorise stem-cell research into cloning for transplantation purposes. In response to this, the UK Government has set up (on 18 August 1999) an Advisory Group to consider possible extensions, particularly in relation to "therapeutic cloning", under the auspices of the Chief Medical Officer.[10]

All research must be licensed by the HFEA,[11] and a separate licence is required for each research project.[12] Before submitting an application for a licence, the approval of an independent ethics committee should be obtained.[13]

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5 s.1(1)(a).
6 Schedule 2, paragraph 3(1).
7 See Schedule 2, paragraph 3(2).
8 Ibid.
9 HGAC & HFEA (1998), paragraph 9.3.
10 See http://www.doh.gov.uk/cegc/press1.htm. The term "therapeutic cloning" is used in the press release.
11 s.3.
12 Schedule 2, paragraph 4(2)(b).
13 HFEA Code of Practice, 4th edition 1998, paragraph 10.7. If the research is carried out within the National Health Service (NHS) then this committee must be an official NHS Local Research Ethics Committee (LREC). Otherwise, the licensed centre may apply to an LREC by prior arrangement or set up its own committee constituted according to parameters laid down by the HFEA (see the Code of Practice, paragraph 10.8).

Embryos may only be used up to the appearance of the primitive streak or 14 days, whichever is the earliest.[14] Written consent is required,[15] which must be from each person whose gametes were used to bring about the creation of the embryo.[16]

Once an embryo has been used for research it must not be used for any other purpose.[17]

Although it is implicit in the specification of permissible purposes that all other purposes are prohibited, the Act nonetheless *specifically* prohibits placing a human embryo in an animal[18] and replacing a nucleus of an embryo with a nucleus of another embryo, another person or subsequent development of an embryo.[19] Furthermore, gene therapy on the embryo cannot be authorised either by a treatment licence[20] or by a research licence, except that in the latter case the Secretary State has the power to pass regulations to permit it in certain circumstances.[21]

Embryos may be stored with a view to research for no more than 5 years.[22] Although regulations can modify this period,[23] none have yet been passed.[24]

The Act came about as a result of recommendations of the Warnock Committee. The Committee was divided over the issue as to whether embryo research ought to be permitted, with only a bare majority (9 out of 16) being in favour.[25] Even the dissenters were divided; one dissenting

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14 ss.1(3)(a)&(4)
15 Schedule 3, paragraphs (1) and 2(1)(c).
16 Schedule 3, paragraph 6(3).
17 s.15(4). This would seem to imply that the embryo may not be implanted after being used for research, and this is how the provision has consistently been interpreted by commentators.
18 s.3(3)(b).
19 s.3(3)(d).
20 Schedule 2, paragraph 1(4).
21 Schedule 2, paragraph 3(4). This power has not yet been exercised.
22 s.14(4)
23 s.14(5).
24 However, for treatment, regulations have extended the maximum period to 10 years. See the Human Fertilisation and Embryology (Statutory Storage Period for Embryos) Regulation 1996 SI 1996/375.
25 Report of the Committee of Inquiry into Human Fertilisation and Embryology, July 1984, Cmnd. 9314, paragraph 11.18.

group was prepared to accept research on surplus embryos but not to allow their creation for research,[26] while another dissenting group was not prepared to accept embryo research even on surplus embryos.[27]

When the Human Fertilisation and Embryology Bill was presented to Parliament, the UK Government, keen to remain neutral on this issue, drafted two clauses—only one of which permitted licensed research. Acceptance of one constituted automatic rejection of the other,[28] and, as stated above, the permissive clause was enacted. Generally, the result has been accepted, and it seems that the passing of the Act has taken much of the steam out of the controversy that raged before it was enacted.

COMPARISON WITH OTHER EU COUNTRIES

Broadly, EU countries can be divided into those that permit embryo research and those that altogether prohibit it. Permission or prohibition, in turn, might be by legislation, other legal means (such as constitutional provision), or solely by non-legal means (such a professional guidelines).

Countries that have enacted specific legislation permitting embryo research under at least some circumstances are Denmark, Finland, France, Spain, Sweden, and the UK.

In Belgium, Greece, Italy, the Netherlands, and Portugal, embryo research has been carried out in the absence of contrary legislation. However, all of these countries are in the process of trying to enact legislation, which in Belgium and the Netherlands, at least, is intended to permit at least some embryo research.[29]

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[26] Ibid., ”Expression of Dissent B: Use of Human Embryos in Research”.

[27] Ibid., ”Expression of Dissent C: Use of Human Embryos in Research”.

[28] See the Human Fertilisation and Embryology Bill. *House of Lords Bills*, Session 1989–1990, Part 1.

[29] Information on the proposed Belgian legislation provided by Guido Pennings, and on the proposed Dutch legislation by Ghislaine van Thiel.
A ”Disengno di legge” (project of law) passed by the Lower Chamber of the Italian Parliament on 26 May 1999 seeks to permit research only for therapy and diagnosis for the protection of the embryo itself. (Information provided by Roberto Mordacci.) Thus, if enacted, this law would prohibit embryo research, as we define it.
We do not have reliable information on Greece or Portugal.

Austria and Germany prohibit embryo research by specific legislation,[30] while it is, in effect, prohibited in Ireland by the provision of the Irish Constitution that the ”the unborn” (presumably from the moment of conception onwards) has a right to life equal to that of its mother.[31]

In Luxembourg, there is no specific legislation. However, embryo research appears not to be carried out.[32]

Those countries that have enacted legislation do not agree on the definition of an ”embryo”. Indeed, unlike the UK, they do not always define it at all. Finland defines it as ” a living group of cells resulting from fertilisation not implanted in a woman’s body”.[33] Germany defines it as a fertilised human egg capable of development from the moment of fusion of the nuclei (and any totipotent cell removed from an embryo defined in the previous manner).[34] While the Spanish legislation does not actually define the term, it refers to general practice regarding a ”pre-embryo” as the fertilised egg up until 14 days or implantation, and the ”embryo” as existing from 14 days to two and a half months.[35] The Austrian legislation does not define ”an embryo” as such, but a definition may be inferred from the fact that the Act covers ”developable cells”, which are defined as inseminated ova and cells developed from them.[36] The Danish, French, and Swedish legislation contain no definitions.

The Council of Europe’s Convention on Human Rights and Biomedicine[37] also does not define an ”embryo”. This was meant to be attended

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30 Act on Procreative Medicine No.275 of 1 July 1992, s.10, and Embryo Protection Act, s.2(1); respectively.

31 8th Amendment, which forms Article 40.3.3.

32 Indeed, we understand that even assisted reproduction by IVF is not available (see Schenker 1997, p.174). Thus, we think that it is unlikely that there will be any guidance.

33 s.2(2) of the Medical Research Act 1999. English translation of the Act in *Bulletin of Medical Ethics*, February 2000, pp.7-11.

34 Our paraphrase of s.8(1) of the Embryo Protection Act 1990. We have used the English translation of the Act in *Bulletin of Medical Ethics*, December 1990, pp.9-11.

35 Paraphrase from the English version of the Official Bulletin of the State No. 282, November 1988, Part II p.5.

36 EGE 1998, p.6.

37 The full title of this is ”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.”

to in a later protocol on embryo research. However, the protocol proved to be impracticable, in part, because the Member States of the Council of Europe could not agree on how the term was to be defined.[38]

All countries allowing research permit it on surplus embryos produced for assisted reproduction by IVF; but all these countries prohibit the creation of embryos for research,[39] except the UK (as stated above). Denmark might also appear to permit the creation of embryos for research (though only for the improvement of IVF),[40] as might the proposed Belgian legislation (which permits creation for research if so decided by a special commission, provided that it cannot be done on surplus embryos).[41] However, the Convention on Human Rights and Biomedicine must be taken into account with regard to those who have signed and ratified it. At present, ten of the EU countries have signed the Convention, of which only Denmark, Greece, and Spain have ratified it.[42] It is our understanding that Austria and Germany have not signed it because it is too permissive, the UK has not signed it because it is too restrictive, and Belgium is unable to sign it due to lack of political consensus with regard to the issues addressed by the Convention.[43]

Although the Convention does not prohibit embryo research, Article 18(1) states that where national law allows research on embryos *in vitro* ”it must ensure adequate protection of the embryo”. The term ”adequate protection” is not defined, but Article 18(2) prohibits the creation of embryos for research.

Article 36 of the Convention allows countries to avoid being bound by certain of its provisions against which they may make reservations. In order for a State to make a reservation, however, the Convention must be

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38 See Lebech 1997, 18.

39 Finland (Medical Research Act 1999, s.13); France (Article 8 of Law 94-654 of 29 July 1994, which inserts Article L. 152-8 of the Public Health Code); Spain (Act 35/1988 on Techniques of Assisted Reproduction, s.3); Sweden (implicitly by Law 115 of 14 March 1991, s.1). We believe this to be true of the proposed Italian and Portuguese legislation, but have no information on Greece and the Netherlands.

40 This, in any event, was the position under the, now replaced, Act of 1992 (see Nielsen 1996, 329).

41 Article 5. Information provided by Guido Pennings.

42 See http://www.coe.fr/tablconv/164t.htm.

43 Information on the Belgian position provided by Schotsmans in an unpublished report prepared for the European Network for Biomedical Ethics: ”Medically Assisted Conception in Belgium: A Commentary on the Legal Framework”, 1998.

inconsistent with pre-existing law in that State. Since none of the three countries that have ratified the Convention have made reservations on the creation of embryos for research under their existing law, it appears that such creation is consequently prohibited in Denmark.[44]

As far as permitted purposes are concerned, Finland is even more liberal than the UK. Research is prohibited only for genetic modification, and even then it is permitted if the aim is to prevent or cure serious hereditary disease.[45] Spain distinguishes between research on viable and non-viable embryos. In relation to viable embryos, research is restricted to diagnostic, therapeutic or prophylactic purposes provided that "non-pathological genetic patrimony is not modified".[46] In relation to non-viable embryos, research is permitted for 10 specified purposes[47] (which basically amount to the same 5 purposes the UK allows in relation to all embryos). Sweden and Denmark[48] only allow research for assisted reproduction by IVF. Finally, France only permits research "exceptionally" for medical purposes, if the research does not impair the embryo.[49] Two medical purposes only are allowed—for the direct advantage of the embryo itself (especially to assist with implantation) or to improve assisted reproduction techniques.[50]

Much like the UK, all countries permitting research by legislation restrict it to within the first 14 days of development of the embryo[51]—except France, which does not specify a time limit.[52]

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[44] This should also be the case with Greece, whatever its proposed legislation says. Spain, in any case prohibits it (see above).

[45] s.15 of the Medical Research Act 1999.

[46] s.15(2) of Law 35 of November 1988.

[47] Which are extendable to any other purposes approved by regulation or the Multidisciplinary National Committee (s.16).

[48] Law 115 of March 1991 and Law 499 of June 1996, respectively.

[49] Article 8 of Law 94-654 of 29 July 1994, which inserts Article L. 152-8 of the Public Health Code.

[50] Decree No. 97-613 of 27 May 1997, which inserts Article R. 152-8-1 to 12 of the Public Health Code. (Information provided by Pierre Langeron.)
The proposed Italian legislation restricts research even more. It must be for therapy and diagnosis of embryo itself, which implies that it must be intended to benefit the embryo. (Information provided by Roberto Mordacci.)

[51] For Denmark, see Law No.460 of 1997 (information provided by Nina Schultz-Lorentzen); for Finland, see the Medical Research Act 1999, s.11; for Spain, see Law 35 of November 1988, s.15(1)(b); for Sweden, see Law 115 of 14 March 1991, s.2 (see Sutton 1996, p.45).

[52] However, the requirement that research be non-impairing *implies* a restriction to a period that is currently well within 14 days.

Finland[53] and Sweden[54] follow the UK position in not permitting implantation after research. On the other hand, Spain (in relation to viable embryos)[55] and France implicitly permit it,[56] while Denmark does so explicitly if there is no risk of transferring genetic diseases or defects.[57]

Finland permits embryos to be stored for research for up to 15 years.[58] France[59] and Spain[60] follow the UK in setting the limit at 5 years (except that the UK permits this to be extended by regulations—which have not yet been passed), while Denmark[61] sets the limit at a year.[62]

IS HARMONISATION NEEDED?

In principle, the laws of the EU countries could be harmonised so that they all prohibit research on embryos (”harmonisation for prohibition”), or all permit research on embryos (”harmonisation for permission”), or they could remain in the current non-harmonised position.

Harmonisation, either for prohibition or permission,[63] requires the agreement of those who are not in favour of that particular development

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53 Medical Research Act 1999, s.13.

54 Law No. 115 of 14 March 1991, s.2. See Sutton 1996, p.45 and Gunning and English 1993 p.164.

55 By not stating that they have to be destroyed and because research for diagnosis is permitted.

56 In this case, by saying nothing and because research must not be impairing.

57 At least this was the case under Chapter 4 of Law No. 503 of 24 June 1992 (see Kriari-Catranis 1997, 58). This law has now been revised and replaced by Law No.460 of 1997 (information provided by Nina Schultz-Lorentzen). As far as we know, the content of this provision remains in the 1997 Act.

58 Medical Research Act 1999, s.13.

59 Article 8 of Law 94-654 of 29 July 1994, which inserts Article L. 152-3 of the Public Health Code.

60 Law 35 of November 1988 s.11(3).

61 See Nielsen 1996, p.328

62 We have no information with regard to Sweden, but suspect that it shares the Danish position, restricting storage to one year.
Under the proposed Italian ”Project of Law”, cryopreservation of embryos would be prohibited. (Information provided by Roberto Mordacci.)

63 The minimum level of concordance required for the achievement of harmonisation for permission, depends on the question that one is asking. Permissivity can range from allowing only non-impairing research (as in France) to allowing just about all research (as in Finland, where only research for genetic modification that is not aimed at preventing or curing serious hereditary disease is prohibited). If one is merely asking whether all the EU countries permit research, and research is defined as we define it, then harmonisation for permission is achieved if Austria, Germany, and Ireland adopt the French position. By contrast, the level of concordance required to satisfy those of a strictly ”pro-choice” persuasion (defined in footnote 67 below) that harmonisation for permission has been achieved would be much higher.
Harmonisation is also a multi-dimensional issue, as countries can agree on some aspects but disagree on others.
We cannot deal with such complexities here, and will treat ”harmonisation for permission” as amounting ”overall” to something within the range of the Finnish, UK, or Spanish positions.

as well as the agreement of those who are. Therefore, in assessing the need for harmonisation, we need to look at the reasons that might be persuasive for both parties. This also provides an indication of the practicability of effecting harmonisation.

The first argument favouring prohibition is moral or religious. It is that human life is sacred and possesses dignity from the moment of conception. The sanctity of life prohibits any research that results in the destruction of embryos, whereas human dignity is alleged to prohibit anything that would ”instrumentalise” the embryo (i.e., use it solely as a means for the benefit of others).[64] Ostensibly, strict adherence to the ”pro-life” position is incompatible with IVF, unless all viable embryos created must be implanted, and this is not the position in Germany and Austria.[65] However, the ”doctrine of double-effect”, according to which it is permissible to do something that one knows will have a morally bad effect provided that it is done with the sole intention of doing something needed to achieve something morally good might be appealed to to justify the German and Austrian position.[66]

The second argument favouring prohibition derives from the proposition that ”eugenics” is to be avoided. This might be a moral argument linked to arguments about the sanctity of life or human dignity. However, it may also have other overtones. Historically, ”eugenics” refers to programmes that are guided by the desire to improve the genetic stock of the human species. Such programmes can be carried out by eliminating ”undesirable” genes (”negative eugenics”) or by introducing ”desirable”

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64 The principle generally appealed to is Kant’s Formula of the End in Itself of his Categorical Imperative:
Act in such a way that you always treat humanity, whether in your own person or in the person of any other, never simply as a means, but always at the same time as an end. (Kant 1948, 91)
Read in Kantian context, persons are setters of ends not merely possessor of interests. However, those who appeal to this principle often extend the principle to encompass beings that merely have interests.

65 As Vitzhum and Kämmerer point out, the German legislation ”neither prevents the creation of surplus embryos, nor can it stop their mass expiration” (1999, 316).
We are unsure whether the creation of surplus embryos, which will not be implanted, is allowed in Ireland.

66 We will not comment on the tenability of such reasoning, and the principle is, in any case, open to various interpretations.

ones (”positive eugenics”). While it has been argued that such programmes are inherently (i.e., regardless of the means used to carry them out) contrary to human dignity, it is extremely difficult to establish this.[67] However, there is little doubt that ”eugenics programmes” have, historically, been associated with highly immoral acts. While this association does not establish that advocacy of ”eugenics” is morally impermissible, it does provide rational grounds for fears that immoral intentions lie behind any activities associated with historical immoral eugenics programmes. It is only to be expected that this will bolster suspicion and rejection of embryo research in Germany and Austria.

Permissive countries, by the very nature of the case, are countries in which these considerations have not proved decisive. In our opinion, the only considerations (apart from moral or religious conversion, or a huge scandal involving embryo research clearly motivated by and carried out in accordance with ”Nazi” type ideals and methods) that might cause these countries to prohibit embryo research are economic or political factors. If this is so, what we must imagine is that the permissive countries regard European Union as an overriding value (politically/economically), and that the prohibition countries are not prepared to associate closely with countries that do not prohibit embryo research. However, both premises are counterfactual!

In permissive countries, a desire for harmonisation for permission might be driven by the moral stance that whatever moral status the embryo might have, it is less than that of born human beings, *to the extent* that not to permit embryo-research would be to deprive those of higher moral status of benefits that they have a right to[68], and that the exercise of these latter rights requires everyone to be able to benefit from embryo research in their own country.

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[67] See Beyleveld and Brownsword 2001, especially Chapter 7. This issue is also explored indirectly in Pattinson 2000.

[68] There are at least two variants of this position, distinguishable on the basis of the level of moral status held to be attributable to the embryo by virtue of the characteristics that it possesses. One position, the ”pro-choice” position, would grant no such moral status to the embryo until birth or beyond. Another position, the ”compromise” position, would grant moral status to the embryo that increases with gestational development until it obtains full moral status at birth or beyond. (See Beyleveld and Pattinson 2000, 249–254, and Beyleveld 2000, 59.)

In prohibition countries, on the other hand, there are a number of factors that might argue for harmonisation for permission.

First, prohibition undoubtedly leads to a disadvantage in scientific prestige, and this might have economic effects.

Secondly, it could be argued that to adhere strictly to a prohibition stance requires not only that one should not engage in embryo research oneself, but should also not take advantage of beneficial products of embryo research carried out by others. On this basis, it could be argued that it is hypocritical to permit IVF (as the prohibition countries do) if one uses knowledge about IVF obtained from embryo research.[69]

Thirdly, and related to this, the strict pro-life position requires those who conduct embryo research involving the destruction of embryos to be regarded as murderers. Countries that permit murder are surely not fit to be associated with in any co-operative enterprises. However, if co-operation is (for some reason) deemed to be justified, then how can one discriminate between those in one's own country that do not share one's moral views as against those in another country? To put it rhetorically, "If you can 'climb into bed' with 'murderers' why can't you have them in your family?"

Arguments for harmonisation need to be set alongside arguments for retaining the non-harmonised status quo.

An argument that has political force for both prohibition and permissive countries is that it is necessary in a plural moral universe to concede at least a degree of cultural sovereignty, either on the basis of national concern as such or, with more moral force, on the basis of the democratic consensus in individual countries.

As far as the permissive countries specifically are concerned, there is the additional thought that non-harmonisation is actually to their econo-

[69] On a similar note, we understand that the prohibition of embryo research in Norway is such that training for use of intracytoplasmic sperm injection (ICSI) is undertaken in the Netherlands.

mic and prestige advantage in relation to the prohibition countries, with whom they then do not need to compete.

Because it should be apparent that the ”natural forces” (i.e., economic and social pressures) are in the direction of harmonisation for permission, non-harmonisation might also appeal to the prohibition countries on the basis that it is the best that can be done to preserve their own principles.

Pulling all of this together suggests the hypothesis that, on the assumption that permissive countries are not wedded to a ”pro-choice” position[70] as a matter of overriding principle, non-harmonisation is optimal for permissive and prohibition countries.

STRATEGIES FOR NON-HARMONISATION?

If non-harmonisation is optimal for both permissive and prohibition countries, it might seem that we have answered the question in our title. Harmonisation is neither needed nor practicable. This, however, is not so. Since the natural forces are in the direction of harmonisation for permission, positive action is required if non-harmonisation is to be maintained.

Essentially, if non-harmonisation is to be maintained, the competitive disadvantage of the prohibition countries must be reduced but not removed. In principle, this could be done by regulation, which would institute an enforced subsidy to be levied on the permissive countries to the benefit of the prohibition countries. The reason why the competitive disadvantage of the permissive countries must not be removed altogether is that this would remove all incentive for the permissive countries to comply. The permissive countries have an incentive to comply with a levy on the premise that not doing so would lead to the prohibition countries becoming permissive with the consequence that the permissive countries would lose more advantage than a levy would cost them.[71]

[70] See footnote 67 supra.
[71] The idea of a subsidy assumes that the economic effects are measurable. They will at the least be difficult to calculate.

However, there are serious legal difficulties with such a proposal. First, direct regulation of medicine or research is not within the current remit of the European Community. Of course, medicine and research are currently regulated by EC Law, otherwise there would be no Medicines Directive[72] or Medical Devices Directives,[73] and it would be impossible to have the pending Good Clinical Practice Directive.[74] However, these Directives rest on being portrayed as internal or common market measures,[75] and it is difficult to see how a subsidy could be portrayed as such.

Secondly, and most seriously, a tax is definitely outside the remit of EC law.[76]

Any policy measures would have to be more subtle. The EC's European Group on Ethics in Science and New Technologies has recommended that the EC not fund research that involves embryo destruction.[77] However, this is unlikely to have much economic effect as researchers in the permissive countries will surely be able to obtain funding elsewhere. But, to be fair to the Group, its recommendation is essentially a moral gesture, rather than an economic policy, motivated by the idea that ethical

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[72] Council Directive of 26 January 1965 on the Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to Proprietary Medicinal Products (65/65/EEC).

[73] Council Directive 1993/42/EEC of 14 June 1993 Concerning Medical Devices, and Council Directive 1990/385/EEC of 20 June 1990 on the Approximation of the Laws of the Member States Relating to Active Implantable Medical Devices.

[74] That is, the proposed Directive on the Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use.

[75] The above mentioned Directives were passed under, or are proposed under, what is now Article 94 of the EC Treaty (previously Article 100) (the Medicines Directive 65/65/EEC) *or* Article 95 (previously 100a) (Medical Devices Directives 93/42/EEC and 90/385/EEC, and the proposed Directive on Good Clinical Practice).
Article 94 of the EC Treaty grants power to the EC Council to "issue directives for the approximation of such laws, regulations, or administrative provisions of the Member States as directly affect the establishment or functioning of the *common market*" (our emphasis). Article 95 of the EC Treaty grants power to the EC Council to "issue directives for the approximation of the provisions laid down by law, regulation, or administrative provision in the Member States which have as their object the establishment or functioning of the *internal market"* (our emphasis).

[76] Since a tax is an anti-competitive measure, it might be thought that this would also incur problems in relation to the World Trade Organisation (WTO). However, countries outside the EU would have difficulty claiming that this measure is anti-competitive, because it would give non-EU permissive countries a competitive advantage over those (permissive or prohibition) countries within the EU, and would not effect the competitive position of non-EU prohibition countries. With regard to the EU countries themselves, we have argued that this measure is actually in their interests, properly considered.

pluralism should be recognised and respected by not funding projects that are at the heart of community dissensus.

CONCLUSION

If our analysis is correct then harmonisation for permission seems to be well-nigh inevitable in the medium to long-term.[78] This is reinforced by the thought that, although harmonisation for permission might not be optimal for *individual* EU countries, it might be optimal for the EU *as a whole* in relation to its competition with the USA[79] and other permissive countries.

The position, therefore, looks bleak for those opposed to embryo research on moral grounds.

[77] See EGE 1998, paragraphs 2.7 to 2.9.

[78] Austria and Germany could become permissive before Ireland. This is because there is more of a moral/religious consensus in Ireland and the Austrian and German stance owes more than Ireland to ”anti-eugenics” (which is likely to weaken with historical distance from the Second World War).

[79] Although federal funding for embryo research is not allowed, embryo research is not prohibited in the USA (at least at a federal level). It might be thought that our arguments ought to apply equally to the individual US States (insofar as they can be classified as permissive/prohibitive). However, it needs to be remembered that the USA is a Federal Republic and that its individual states do not compete as States in the way in which the EU countries still do.

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5. PERMISSIBILITY OF EMBRYONIC RESEARCH

Jacek Hołówka

The beginnings of a human life are clouded by uncertainty. It is hard to say when a human being begins to exist. Is it at the moment of conception, when the primitive streak appears, when its neurons begin to operate as an integrated system, when the child is born, or when it acquires the sense of being alive, whatever the last qualification may mean? Depending on which of these positions we adopt, a human being begins when the zygote is formed, when it has been attached to the womb, when the embryo has developed, when it has changed into a fetus, or when the fetus becomes a child. Doctors have a sound knowledge of this process but it can not help us directly to decide when a new human being starts its existence. It seems obvious that the typically human characteristics are acquired gradually and that the process goes on long after the child was born all through the formative years of its development. But our emotions and imagination do not permit us to accept the view that being human is a graded condition. This is slightly amazing. We are accustomed to the idea that in the case of insects, a caterpillar turns into a chrysalis and a chrysalis changes into an imago. Nobody tries to argue that a chrysalis is a crumpled insect, or a caterpillar is a disguised chrysalis. The recognition of intermediate stages poses no problems to us. A caterpillar is a separate entity, and so is a chrysalis and a mature insect. In the case of humans we are unwilling to adopt the same attitude to gametes, zygotes, embryos and fetuses. We insist on speaking in dualistic terms that do not allow for the existence of intermediate phases. A particular organism is, or it is not a human being, but it can be nothing in between. It can not be an incipient human being, a future human being or a specimen of the human species that is not yet a human being.

Let us see what is specifically wrong with this attitude. The problem is neither that we hesitate to decide when a human being begins to exist, nor it is the fact that we refuse to admit that "being human" is a predica-

te that allows for gradation. The problem is that some conservatives use the term "human being" in two different and confusing senses. In one sense the term refers to every organism that belongs to the human species. In another, it refers to individuals that have human rights and should be treated as human persons. Those who conflate these two senses assume that because a given organism belongs to the human species it possesses human rights. As a consequence they claim that human zygotes or embryos possess the same rights as those that belong to human individuals who truly possess these rights. No medical, ethical or philosophical reasons can be adduced in support of this simplistic approach. We sufficiently understand relevant medical facts to know that embryos do not suffer, do not form decisions, do not have preferences and in general are fully unconscious. So we can also see they can not have rights in the sense in which sensitive human beings have rights. We may be strongly motivated by religious, emotional and cultural considerations to treat embryos with respect that is not normally accorded to members of other species or inanimate objects. But these considerations are open to challenge and revision. If they clash with rights and expectations of mature human individuals we must use better criteria than traditional attitudes and emotional habits. We find it difficult to form a well thought-out attitude to embryos, because in general we are confused and uncertain about our obligations to higher primates, disabled persons, fetuses, human images and ghosts. We do not know how to treat them because they resemble humans enough to stir our emotions but not enough to make our mind believe that they really are what they seem to be--something very much like ourselves.

For very similar reasons we feel uneasy sometimes when we speak with our own grown up children. We do not quite know how to treat them. We would feel more comfortable if we could put them into one of the rigid categories that we already know how to handle. Sometimes we want to treat them like our old little babies, sometimes we can only see fully mature strangers in them. It takes some time before we learn that they are something different from either category and that we must develop a new attitude to them. The same is true about embryos. They are neither full

human beings nor pieces of living tissue, and we must engage in deliberation to decide how we should treat them.

These difficulties loom large from the very beginning, when a distinction is drawn between surplus embryos that were produced for the purpose of being implanted but have not been selected, and those that might be produced specifically for the purposes of scientific research and without any chance of being implanted.

> The British IVF pioneer, Robert Edwards, reports unease at the suggestion that embryos should be specifically created for research. He claims that this unease arises when considering the intention behind creating an embryo for research, as distinct from the one behind using surplus embryos. (Gerrand 1993: 180)

Obviously, if an embryo was a distinct human being with human rights, then using it for research would be like sacrificing limb or life of a mature individual for anatomical study. We would find it abhorrent and impermissible. If, on the other hand, an embryo were a lump of human tissue combined into an organism, then all qualms about its mistreatment would have been misplaced. As most of us would agree that an embryo is neither a bundle of organs, nor a separate human person, but something intermediate, we must find a new solution. We can do so by studying two initially opposite positions.

> (1) If there are spare human embryos that are not viable, (e.g. they have been retrieved from ectopic pregnancies) there are no reasons to demand that they are annihilated rather than used in research.
>
> (2) It is unacceptable to create potential human beings for the sole purpose of using them in research and never allowing them to become human beings. (Gerrand 1993: 177)

Consider position (1). If we already have a legitimately acquired embryo, say, one that has been derived from a spontaneous abortion, it

seems that only two options are open with respect to its future--it can either be thrown into an incinerator or it can be used in research. If we say we would rather throw it in an incinerator because we would not allow for its being used for any utilitarian purposes, our position would sound callous and unreasonable. Our only defense would be to claim that we assign to embryos such elevated status that they are something holy and divine for us that can never be used as a means rather than as an end. Some primitive tribes display this attitude with respect to their dead. The practice was studied by Sigmund Freud and we will return to it. At this point I will only say that most reflective people do not permit themselves to be guided by such feelings, so they will probably agree that embryos that have been legitimately acquired may be used for the benefit of science and society.

Now consider position (2). How can it be supported? What is wrong with creating additional embryos for the sole purpose of using them in research laboratories. Is it really better that an embryo does not exist at all than that it is created for the advancement of science and medical practice? Some conservatives would say, yes. It is better--they claim--never to come to exist as an embryo, than to become an embryo subsisting *in vitro* without a chance of being implanted and developed into a full human being. Again the main reason for this attitude can be found in the claim that embryos are holy and divine, and therefore must not be treated as a mere means. But position (2) is usually put forward in order to make an additional point that deliberate creation of research embryos is morally worse than neglecting surplus embryos. It is important to see that this claim can not be sustained. It is true that viable embryos have a chance to be implanted, whereas surplus embryos do not. But we do not value chances as such. They are only instrumentally important to us as something that leads to desirable results. The fate of an embryo that had a chance of being implanted, but was not, is no different from the fate of an embryo that never had that chance. So we do not have good ethical grounds for distinguishing between two kinds of *in vitro* embryos, the surplus ones or the research ones. If it is acceptable to use surplus embryos, it is acceptable to create them in order to assist research and therapy.

> It is difficult to see how the argument from potentiality would yield different conclusions with respect to those embryos created for research and using those which are surplus. (Gerrand 1993: 177)

The foregoing remarks have shown--I believe--that the status of embryos should not be differentiated with respect to their prospects of implantation. they have also shown that the status of embryos can not be determined by medical or biological facts and that it can not be established by a simple transfer of human rights on human organisms before they have been born. This means that the status of embryos does not belong to *questiones facti* but to *questiones pacti* and it must be determined by other considerations that we will now have to review.

THE NEED FOR RESEARCH

Scientists seem to agree that research on embryos is very important for the development of the medical sciences and new methods of treatment. Various examples are given to support this view. Through experiments on embryos it was possible to develop measures that lessen the maternal-fetal HIV transmission. Similar research is necessary for developing possible treatment of congenital diseases. (Brody 1998: 100) Fetal kidney tissue was used in a research that led to the culturing of the polio virus and the development of the polio vaccine. (Brody 1998: 103) Embryos are used in screening products for toxicities and carcinogenesis. The tissue derived from embryos is helpful in treatment of diabetes and neurological ailments such as Parkinson's and Huntington's diseases. (Brody 1998: 103) Though it is often required that fetal research is undertaken only after appropriate experiments have been conducted on animals, it appears that initial fetal research is necessary in order to be able to create animal models for human diseases. Essentially embryo research is fundamental in the study of pathological pregnancies and their treatment. Baruch Brody mentions several kinds of projects based on embryonic experiments--research to improve the success rates of IVF, research on preim-

plantation genetic diagnosis, research on isolating pluripotent stem cell lines for eventual differentiation and clinical use in transplantation, research on nuclear transplantation to avoid disorders due to maternally inherited cytoplasmic defects, basic parthenogenetic research of the role of maternal and paternal genetic material in development of fetuses, basic research on fertilization and early zygote development. (Brody 1998: 103) Other authors concur.

> [S]uch research will give information about the processes of fertilization and embryo development in its very early stages. Furthermore, embryo research may help to improve *in vitro* fertilization and other reproductive techniques. Indeed, it has been argued that if embryo research is not allowed, there is little point in continuing the IVF program. (Gerrand 1993: 175)

Moreover, it is emphasized that fetal tissue can not be replaced with other materials, because it possesses some specific properties that can not be found in other tissue:

1. It develops rapidly, hastening desired effects
2. It is less antigenic, minimizing rejection problems
3. It is more resistant to damage both in vitro and after transplantation
4. It is potentially in a large supply from elective abortions. (Brody 1998: 103)

RESEARCH PRACTICE

Nobody objects to the practice of conducting therapeutic research on fetuses. The question becomes more difficult when the expected therapeutic effect is uncertain or insignificant whereas the scientific benefit of the research is more certain. It is usually assumed that non-therapeutic research on fetuses is allowed only (1) when the risk to the fetus is "minimal", and (2) when the research is undertaken after the completion of similar studies on animals.

It is striking that both the US standards and the Council of Europe standards for acceptability of research on fetuses are stricter than restrictions concerning research on children, where normally the "minimal harm" clause is not included. No explanation of this difference has been offered, and its adoption seems *prima facie* ungrounded.

> The justification for these stricter requirements on nontherapeutic research involving fetuses than on nontherapeutic research involving children is unclear. (Brody 1998: 101)

It is conceivable that in the future this discrepancy will be noted and removed by appropriate national and international legislative bodies. The question remains, however, which way it should be corrected. Is it better to make research on children more difficult and restrictive, or is it better to make requirements allowing for research on embryos more lenient? This problem must not detain us here, though it is essential for legislators. It is more interesting to inquire, why this difference was introduced in the first place, i.e. why legislators wanted to accord to embryos a higher protection status than they have accorded to infants. One possible explanation is that until recently medical professions tended to neglect pain occurring in small children. It has been commonly believed that we do not know enough, why children suffer, and when, or what can be done to alleviate their pain. The use of analgesics seemed dangerous, so the problem was dismissed by saying that a large proportion of crying in infants has no clinical explanation.

A different answer is suggested by Paul M. McNeill, who lists the restrictions that are normally in force when experiments are conducted on human beings. We require (1) that individuals with diminished autonomy receive special protection, (2) that subjects are respected as persons, which means that they are informed about the proposed experiment, its duration, objectives and expected results, (3) that some form of consent from the subject is obtained before the experiment can begin, (4) that the benefits should outweigh the risks, and (5) in case of a controversy a body of decision makers will be set up to choose which is more important, the need for research or the need for the protection of the subject of experi-

ment. (McNeill 1993: 139-156) In the case of embryos that have no autonomy and no understanding of their situation, none of these conditions can be satisfied. That probably gives researchers bad conscience, because they are unable to demonstrate their willingness to proceed with caution and compassion. To allay their unease some researchers may welcome the cryptic formulation that the risk to the fetus is "minimal", even if they know that the fetus will die in the experiment. A still different explanation can be found in the writings of Sigmund Freud on taboos. Consequently reputable institutes adopt some protocols that usually include some the following points:

1. The issue of tissue donation by a pregnant woman should only be raised subsequent to the decision to have an abortion.
2. No financial inducements should be offered to the pregnant woman nor may she specify the use to which the tissue will be put.
3. The timing and technique of the abortion should not be influenced by the decision to donate the tissue.
4. Separate physicians should be involved in the abortion and in the fetal tissue research. (Brody 1998: 106)

These precautions are adopted to demonstrate that researchers do not encourage women to have abortions. They also absolve the researchers of the possible blame for suggesting to women that they can profit from delivering human eggs or embryos for research. They may also counter the intimation that embryo research is a cruel practice, comparable to the most irresponsible treatment of humans ever known.

> Many of the discussants of this question appeal to the analogy of the appropriateness of using data from illicit human experiments [...] such as the Nazi experiments that give rise to the Nuremberg Code. (Brody 1998: 108)

It shall be clear that if such protocols are observed, the comparison is totally ungrounded. The differences are obvious. The practice of provi-

ding eggs or embryos is voluntary, it is conducted competently and presumably leads to the development of new preventive and therapeutic methods, the participants are not threatened by enslavement or torture. One should also bear in mind that most eligible women will not be ready to provide eggs, to say nothing of embryos, because the procedure for acquisition of such substances is connected with an immense violation of privacy.

> [W]hen the women involved are the focus of concern, significant moral problems arise. In particular the autonomy of these women is being undermined when we consider the hormone stimulation therapy and invasive procedures that they need to undergo in order for the eggs to be obtained that are needed for the creation of embryos. (Gerrand 1993: 186)

This indicates that the number of eggs that are available for study when the restrictive protocols are in force will be rather low and will not have a detrimental effect on public morality. The opposite difficulty may arise. The number of eggs may be so low that it will be impossible to sustain medically important research projects. Consequently some researchers have already pointed out that they will not observe all the four points of the cautious egg acquisition procedure.

> The Swedish investigators of transplanting fetal neural tissue reported in *The Lancet* the modifications they adopted to the standard suction technique to ensure that fetal tissue would not be macerated; a similar modification was reported in The New England Journal of Medicine in 1992. (Brody 1998: 107)

This is a potentially disturbing development, but it concerns the practice of acquiring eggs and treating the donors, not the question of permissibility of embryonic research as such.

OPPOSITION TO RESEARCH

It is understandable that confused emotions, controversial practices and inconsistent legal regulations may induce some persons to launch an

attack against embryonic research, and to reject it in principle. This opposition has to be expected and must be met undertaking a serious discussion on the moral status of human embryos.

The strongest opposition to embryonic research comes, however, from advocates of the belief that all human beings are the work of God and as such are perfect. Any attempt to tamper with the process of human growth and development is consequently blasphemous. This belief is most characteristically expressed in the statement that human organisms are from the very beginning human persons, with all privileges and rights that belong to persons.

> The instruction of the Congregation for the Doctrine of Faith formulated in 1987 reads: "The fruit of human fertilization, from the first moment of its existence, i.e. from the moment when a zygote is formed, morally deserves an unconditional respect that is due to the human being in its corporal and spiritual integrity. The human being should be respected and treated as a person from the moment of conception, and therefore from that moment it should be granted the rights of a person, and among these rights, in the first place, the inviolable right of every innocent creature to exist". And additionally: "The embryo should be treated as a person". (Voraut 1989: 63)

Proponents of this position are aware that it is in a bad need of a logical support, so they offer some arguments in its defense. The usual stratagem is to put together various opinions that are quoted fragmentally and make them appear as a consistent whole.

> So much has been confirmed by the Warnock Commission: "Once initiated the process of development does not contain special phases, different from others. They are all integral parts of a continuous process". The proposition that a human being is a person from the moment of the formation of the zygote is confirmed biologically and logically. The crucial stages that mark the gradual formation of the brain structures are evolutionary thresholds that signify the structure of an individual, but they potentially

> exist from the moment of fertilization. This continuity sustains the belief that the zygote, embryo and fetus are successive stages in a development of the human body that comes from a human body. Freezing can interrupt that process for a certain time or forever. But the relationship between fertilization and pregnancy does not effect the status of the human embryo. (Voraut 1989: 63)

From the fact that it is difficult to distinguish clearly defined phases in the development of the human organism--which is a well known biological fact--it is concluded that "a human being is a person from the moment of the formation of the zygote," which is highly questionable. Then this dubious assumption is presented as a fact that has been "confirmed biologically and logically," though obviously neither biology, nor logic, can decide that a zygote is a human person. To such conservatives being a human person is a question of fact and not a question of theoretical construction or convention.

On these premises advocates of embryonic inviolability reject not only embryonic research, but also elective abortion and, possibly, *in vitro* fertilization.

> Even if abortion does not meet with penalty, it still remains a crime. (Voraut 1989: 70)

To win acceptance of their views they present them as widespread and supported by serious moral authorities. Jean-Marc Voraut pretends, for instance, that Jesus Christ and Immanuel Kant shared his opinions.

The dignity of a man and his body, starting from an embryo that awaits humanization and ending with a diseased corpse that bore the name of man, raises against the slowly emerging logic of science that liberates itself from ethics. To quote Kant: "What has a price can be freely exchanged for something else as its equivalent. But what is priceless, and therefore lacks any equivalent, possesses dignity". Such is the gift of life, with respect to which the words of Christ resound with full clarity: "Verily I say unto you, Inasmuch as ye have done it unto one of the least of these my brethren, ye have done it unto me". (Mt 25, 40) (Voraut 1989: 71)

It is certainly right to say that a human being was priceless to Kant. But it begs the question to add that Kant subsumed under this category fetuses and embryos. But it is as good as frivolous to claim that by "the least of these my brethren" Christ meant zygotes and fetuses.

A completely different argument is sometimes used in support of the opinion that experiments on zygotes are unacceptable. It relies on the alleged power of logical consequence. Two mutually opposing views are assembled, a traditional one and a liberal one, and it is said that one must espouse them wholesale or reject them wholesale. Rosalind Hursthouse has made an interesting tabulation of such extreme positions. (Hursthouse 1987: 47, 58)

	The Traditional View	The Extreme Liberal View
Abortion (at any stage)		
(i) to save the mother's life	(possibly) permissible	permissible
(ii) on social or psychological grounds	Impermissible	permissible
(iii) as fetal euthanasia	(possibly) permissible	permissible
(iv) to avoid a child with a disability	impermissible	permissible
Fetal research		
(i) on live fetuses	impermissible	permissible
(ii) in dead fetal tissue	(possibly) permissible	permissible (with the woman's consent)
Breeding fetuses for the purposes of research	impermissible	permissible
In vitro fertilization and embryonic research		
(i) creating embryos and deliberately allowing them to die	impermissible	permissible
(ii) keeping embryos as living tissue for the purposes of research	impermissible	permissible
Infanticide	impermissible	(probably) impermissible (infanticide of premature babies possibly permissible)

In this proposal it is assumed that any argument in defense of any specific point on the lists is irrelevant, because the strength of the position derives from its cohesion and consequence, not from the strength of its individual elements. Consequently if the list is made stronger, its validity is allegedly reinforced and the position may serve as a foundation for even more dubious claims.

> According to the conservative view, the fetus is in most if not in all morally relevant respects like an average adult human being from the moment of conception. This is sometimes expressed as the view that „human life begins at conception or fertilization“, or that what we have from the moment of conception is, as I have heard it said, "not just a potential human being but a human being with a potential". (Hursthouse 1987: 31)

Some conservatives take this interpretation both seriously and literally, even though it leads to some consequences that do not please them.

> Suppose a madman has got hold of a baby in one hand and a ten-day-old embryo in a test-tube in the other, and is about to kill them both. Suppose you can only save one of them. On the conservative view there is no intrinsic difference between the two which would ground your saving the baby rather than the embryo. (Hursthouse 1987: 31)

If it is put to the conservatives that their position is not sufficiently sensitive to the differences between zygotes and children, they respond by saying that our moral intuitions sometimes fail us. If we want "to break the tube and spare the child" we are unduly sentimental. It is the question of logical consistency to accept consequences of one's initial choices even if their consequences are incompatible with widespread moral intuitions. If one opposes to elective abortion and embryonic experimentation, one has to agree that there is no moral difference between an embryo and a baby.

But obviously logic can lead people either way, to choose a consistent conservative option, or to choose a consistent liberal option. As a matter

of fact, no logical fault is involved even if we choose a mixed position, as long as we clearly and consistently define it. We may say that experimentation is permissible until, for instance, the primitive streak appears or until the neural system begins to function as a single unit. Nothing in logic would tell us that our position is wrong. Huge tables break under their own weight rather than support convincing positions.

EMBRYOS AS TABOO

In the spirit of John Locke we can say that whenever an attachment to a chosen position is stronger than the reasons that have been put forward in its support it is motivated by other considerations than those that have been given. If additionally the selected position is presented and defended with a sense of awe, we can suspect that it is marked with neurotic traits. Sigmund Freud noted a similarity between belief in taboo and neurotic obsession. If we are exposed to ambivalent feelings that are so strong as to overpower our mind, and if we can not resolve the emotional conflict with calm explanations, we will not be able to control all our opinions. In a social group the suppression of the troubling issues turn them into taboos surrounded by various magical routines. In an individual the suppressed contents will make man turn against himself by developing a neurosis.

In many cultures taboos are connected with death. Understandably, it is a shocking experience to see a living person stop breathing and become a corpse. The episode evokes conflicting feelings. The witness would like to revive his kinsman and continue to treat him or her as he did before, but he realizes it is impossible. The deceased person will not respond and will not sustain the emotional, interactive ties that connected them in the past. The witness may see this as a very hostile and threatening attitude. In some primitive societies death is accentuated with an immediate change of the name of the deceased person.

> The avoidance of the name of the deceased is as a rule kept up with extraordinary severity. Thus among many South American tribes it is considered the gravest insult to the survivors to prono-

> unce the name of the deceased in their presence, and the penalty set for it is no less than that for the slaying itself. [...] The Masai in Africa have hit upon the evasion of changing the name of the deceased immediately upon his death; he may now be mentioned without dread by this new name, while all the prohibitions remain attached to the old name. [...] The Australian tribes on Adelaide and Encounter Bay are so consistently cautious that when a death occurs almost every person who has the same name as the deceased, or a very similar one, exchanges it for another. (Freud 1938: 95)

Freud found European patients who had symptoms very similar to those displayed in American and African tribes.

> As was to be expected, the compulsion neurotics behave just like savages in regard to names. They show the full "complex sensitiveness" towards the utterance and hearing of special words (as do also other neurotics) and derive a good many, often serious, inhibitions from their treatment of their own name. One of these taboo patients whom I knew adopted the avoidance of writing down her name for fear that it might get into somebody's hands who thus would come into the possession of a piece of her personality. (Freud 1938: 97)

The explanation that Freud has offered emphasizes the ambiguity of feelings rather than the sense of confusion. He may be right or wrong about that emphasis, but what matters here, is that when members of a tribe face a dead person they do want to treat him or her neither as an object nor as an enemy, but at the same time they can not treat him as a living relative and an old friend. The sense of a loss is augmented by the understanding that what has been done has been done. Nothing will bring the dead one to life again. The witness may hate himself for his inability to cope with the situation, and in some tribes one or two persons are delegated to bury the dead. Ever since their bear the symbolic blame for the death. The grave diggers become taboo, and the dead person becomes reprehensible to them, even though they took it upon themselves to bury the dead.

> Such hostility hidden in the unconscious behind tender love, exists in almost all cases of intensive emotional allegiance to a particular person, indeed it represents the classic case, the prototype of the ambivalence of human emotions. There is always more or less of this ambivalence in everybody's disposition; normally it is not strong enough to give rise to the obsessive reproaches we have described. [...] The disposition to compulsion neurosis which we have so often taken for comparison with taboo problems is distinguished by a particularly high degree of this original ambivalence of emotions. (Freud 1938: 103)

The parallel between a corpse and an embryo is obvious. Both are an extension of a live, fully developed human being. One extension is live but not yet developed, the other is fully developed but no longer alive. We can be deeply moved and confounded when we have to face such hybrid entities. Our confused feelings may be relieved if we resort to mysticism, magic, neurosis or bad logic. We need to be more secure, we will create taboos about corpses and embryos, and we will refuse to treat them for what they really are, i.e. incomplete human beings. The concept of an incomplete human being is so jarring, repelling, and to some people utterly incomprehensible that a lot of effort is made to get rid of it.

CULTURAL ABHORRENCE

But it is possible to develop a more balanced attitude that probably should be called a liberal one. Liberals are abhorred by the prospect of harming sentient beings and they disapprove of certain proposals in genetic engineering. It seems impermissible, for instance, to create cross-species individuals, especially if they involve human genes. It is objectionable to experiment on zygotes with a view of creating human monsters or superhumans. It is *prima facie* immoral to implant modified zygotes in the wombs of women, even if they consent to the test. And it is *prima facie* unacceptable to undertake engineering manipulation that might result in destroying the pool of genes in any species.

Some of these objections can be explained by naturalistic reasons, but some not. What is specifically wrong with creating a happy breed of monster, say, pretty mermaids with discreetly concealed gills?

The answer has to be given by installments. First, on the naturalistic or liberal view, it is not absolutely wrong to create such specimens. We can imagine a situation when it is not wrong to create a breed of mermaids and water boys. Suppose a nuclear catastrophe radically reduced the amount of oxygen in the air but not in the sea water. If it were possible in such a situation to produce a new breed of humans that would live happily in the water, the option would be preferable to a total extinction of mankind. But barring such catastrophic developments, we have no reason to accept the idea that a breed of half human creatures is created, even if they were happier than we are. J. S. Mill's preference for an unhappy Socrates still sounds right. Happiness at the cost of imbecility or monstrosity is not an attractive goal. Let us see why.

We have all grown up in a culture that is in a great part responsible for our mental and physical make up. Perhaps if we had grown up in a different culture we would have been more flexible and we would have felt more at ease in the company of monsters and mermaids. But as things are, our limitations are constitutive of our nature and we would rather be unhappy humans than happy products of genetic engineering. Admittedly this preference is irrational, but at the same time it is deep seated and almost religious. Moreover it is by no means motivated by a taboo. If we saw a mermaid, we would be confused but we would know she must be treated with equal respect to the respect we show an average human being.

Every culture is based on certain values that may not be directly perceived, but which are responsible for our collective identity and collective life plans. Leszek Kołakowski calls such values symbols, and sometimes, I think, he is even prepared to call them religious symbols.

> Anything can become a religious symbol: a man, a word, an individual biography, every object, a stone, a building, an animal, a relic. But nothing can be turned into a religious symbol by a ratio-

> nal agreement, by a free contract or an arbitrary design. An object can acquire a symbolic power only if a congregation of the faithful has bestowed on it this particular status in a spontaneous and authentic concordance. A religious symbol can be no more imposed by an efficient method of persuasion than, for instance, a symbol incarnating national values of a given community. (Kołakowski 2000: 224)

The difference between medical research on embryos and genetic engineering is connected with the fact that we do not have traditional inhibitions against experimenting with fetuses, whereas from times immemorial, when myths and fables were passed from generation to generation, we were scared by demons, centaurs, satyrs, Minotaurs, ugly witches and Quasimodos. Being a monster is a symbol of misery, misfortune and a beastly abnormality. We can call the natural dread of such creatures childish superstition, but the imagery surrounded by this fear is something more than a folklore theme. It is a powerful cultural symbol, a pattern that runs through the fabric of our culture. Perhaps we would be going too far if we said that our social existence is woven from this fabric, but it seems clear that we can not tamper with it frivolously if we wish to be saved from social anomie and disorientation.

> [S]ymbol can not be freely replaced. It is conceivable that an international convention can declare that the blue color rather than the green will henceforth signify the right of way, if, for whatever reason, the blue color is found more convenient. It is unthinkable, however, that the pope in a flight of frivolous inventiveness declares that a triangle or a rosette rather than the cross will henceforth symbolize Christianity. (Kołakowski 2000: 223)

The lesson to be learned here is that we must distinguish between cultural symbols and neurotic fears. The vision of a laboratory that produces cross species monsters is terrifying because it violates cultural symbols, not because monsters are hideous and make us uneasy by their appearance. The vision of a laboratory experimenting with cultured embryos violates no cultural symbols, because it is a new proposal with benign con-

sequences. It stirs our emotions because we do not know where we should draw the line between acceptable and unacceptable experiments. We are worried by our personal confusion and indecision, and not by the prospects of eroding the culture in which we grew up. On the other hand, protests against irresponsible cloning of humans or against new breeds of man incite fear of a complete change of the world we live in. They reveal to us some elements of our mental heritage and make us understand that they can be threatened. We do not want scientific and technical advancements to trample upon symbols that are part of our cultural tradition. Seemingly similar protests against experiments on embryos can not be justified in this way. Non-therapeutic research does not undermine our tradition values, does not change the culture we share. The opponents of embryonic research use their arguments against their better knowledge, because they are motivated by a neurotic anxiety and not by an attachment to the common background. They make an illegitimate equation between human persons and human organisms and try to profit from the fact that it is usually difficult to perceive the true source of social uneasiness and apprehension.

It is conceivable, of course, that one can be genuinely unaware of the origin of one's fear. But in general, it is possible to perceive the difference between cultural symbols and the troubling visions of a neurotic imagination.

> Symbols [...] are an instrument of communication, but they are not, so to speak, encrypted messages that reveal something that could be expressed differently. What they disclose in an act of communication is, in a certain way, monopolistic, because they also incarnate a piece of the world, they are its bearers, carriers and representatives. They constitute a tangible testimony to a specific manner of seeing the world, and apart from the perception of a symbol, there is no immediate perception of the world. (Kołakowski 2000: 222)

The last words are very important. We can not help but see the world through symbols. The prospect of doing unjustified harm to a human

being evokes in us moral revulsion and a sense of injustice. The prospect of experimenting with human embryos confuses our mind and makes us feel uneasy. These two classes of feelings have to be clearly distinguished, because the former is rational, the latter neurotic.

LEGITIMATE SACRIFICE

The official policy adopted by international bodies whenever a troubling ethical question is raised is to seek a compromise. This may be a good policy on pragmatic grounds. It is also a good solution when various parties fight for their interests. It is not a good solution when the problem to be solved arises form an emotional or intellectual confusion. A compromise makes the confusion even more hopeless.

> The real problem is that we lack any good understanding either of the value of moral compromises in shaping official policies or of the standards for a good moral compromise. Too often, the fashioning of a compromise-based official policy is viewed as a political necessity and the terms of the compromise are dictated by the counting of votes. (Brody 1998: 117)

The problem of embryonic research can be viewed as a conflict of interests between research companies and research subjects. But we should not assume that this conflict is insuperable or, as Paul McNeill points out, that society must side with either party.

> In experimentation on human subjects, society cannot be assumed to be aligned with the interests of either science or the subject. It presumably has an interest in both. (McNeill 1993: 167)

It is not clear, at first glance, how far this social interest goes. Society does not hold individuals sacred. It is interested, for instance, in sustaining its independence and in defending itself against enemies. At the time of war ultimate sacrifices are demanded from soldiers who must give their time, health, skills and sometimes life for their country.

> War has been used to justify much gratuitous cruelty in the name of science [...]. However, there is no good reason for exempting

> experiments on human subjects in wartime from the same principles that apply in peacetime. The issue is whether the risk of harm to these particular subjects can be justified by the potential benefit to others. [...] In my view, even the exigencies of war do not vindicate the deliberate and knowing exposure of human subjects to extreme risks of harm in an experiment designed to test the effectiveness of weapons. (McNeill 1993: 169)

McNeill alludes to the case when commanders in Australia recruited their own troops for some experiment involving mustard gas, before they decided to test the gas against the enemy. The wisdom of such a procedure is very doubtful, of course, but the question raised by this case has a broader significance. Why is war so different from peace? If it is permissible to send out troops to an almost certain death, why should it be morally unacceptable to send out embryos to a certain death as long as they feel nothing, hear nothing and do nothing? But assume that the opposite answer is correct, that it is immoral to send out troops to an almost certain death. Is it then also unacceptable to create cultured embryos for research?

The answer is no. The wrong thing when a soldier dies is not that a human organism ceases to exist, or that the world will now miss one more human being, but that a human life plan has been ruined, a life plan that was designed and carried out by a sentient individual who put a high stake on its full realization. We can not say the same thing about an embryo, which has no plans of its own, and is certainly indifferent to its future before it can have any mental images. So we do not need to look for compromises when we need rules that should guide us in embryonic research. These rules should be based on clear philosophical arguments, and not on feelings or neurotic fears.

CONCLUSIONS

Let us see what moral and philosophical arguments have been reviewed so far and found reliable.

(1) We did not see any reason to distinguish between the moral status of surplus embryos and the moral status of research embryos.

(2) The proposal to produce human embryos for research is rejected by conservatives on the grounds that are vague or based on the concept of taboo. These are not good grounds on which to base socially binding decisions.

(3) It is clear that if ectopic pregnancies and spontaneous abortions are the only source of eggs and embryos, the supply of the required material will be too limited to continue well organized researches. This is sound practical reason to make production of research embryos permissible.

(4) Legal institutions that are created to solve such issues are brought to a standstill by poorly articulated controversies. In the attempt to find a compromise they try to suit several parties at the same time and produce cryptic pronouncements together with unhelpful declarations. One such declaration is, for instance, the decision of the Council of Europe contained in the *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* (1996; Article 18) which reads: "Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo". Obviously no such protection is possible if research is permitted.

(5) The law making institutions may claim the right to defend basic values of the dominant culture, but they should make sure that they are not acting on behalf of a partisan and narrowly defined view of that dominant culture. The cultural symbols that they will want to defend must be commonly recognized symbols of all traditions within the culture.

If these philosophical arguments are accepted, it seems possible to formulate three rules of thumb that can be useful in the field of embryonic research.

(1) It is wrong to inflict harm and cause pain. This rule does not apply to embryos, because they are unable to suffer and form life plans. Though they may develop into organisms that will have full human rights, they do not possess these rights before they have developed consciousness.

(2) It is *prima facie* right to assist people in their efforts to carry out their life plans. This rule applies to embryonic research and indicates that the research is permissible in most of its forms. It can produce therapeutic substances and prevent congenital abnormalities.

(3) It is important to respect cultural conventions and traditions, even if their utility is not immediately clear. But symbols are less important than suffering human individuals and should be distinguished from neurotic fears. Moreover, cultural values change in the course of time, and undermining some of them does not constitute a serious threat to culture as such.

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6. Preimplantation Genetic Diagnosis (PGD)[80] and Embryo research

Hans Lilie

The legalisation of preimplantation genetic diagnosis and embryo research, which has recently given rise to the most serious misgivings, is now under intensive discussion. The legality of artificial reproduction is becoming more and more doubtful, so that the atmosphere is strained and emotionalized. The main point of the argument held by the critics of preimplantation genetic diagnoses (PGD) is that it abandons the commitment to protect unborn human life and thus opens the way to a process of selection being applied to human embryos.

Selection procedures involving human life immediately remind us of the terrible experiences suffered in Germany during the time of the Third Reich and consequently very wary discussion is required. One of the most imminent problems is that physicians are pressing for permission to fertilise and implant human embryos, while reserving the right to abort these embryos afterwards if certain pathological results are diagnosed. Therefore, especially in Germany, preimplantation genetic diagnosis is discussed as a biomedical procedure involving decisions over life and death. Thus the discussion is addressing questions that are of general public concern and which, therefore, are a matter of law. Critics of the procedure doubt whether PGD is permissible by law. One widespread suspicion is that the German legislature will be trapped in a labyrinth of court cases. It is argued that the new possibilities to choose between wanted and unwanted human beings will pave the way to a programme of undesirable embryo research and a kind of new eugenics.

Since our culture is devoted to the protection of human life, this opinion, which opposes every form of preimplantation genetic diagnoses, would

[80] See also Schneider, Auf dem Weg zur gezielten Selektion, Strafrechtliche Aspekte der Präimplantationsdiagnostik, MedR 2000, S. 360.

appear to be cogent. It seems to be founded on the German Law on the Protection of Embryos. Whereby, they claim, according to the spirit of this law, a fertilized, potentially human egg cell from the very point of fertilization as well as every totipotent cell extracted from an embryo and able to develop into an individual are to be defined as EMBRYOS. Therefore, extracting a totipotent cell from an embryo and using it for PGD is not permissible by law[81]. At present, especially the further fate of the embryo must not depend on the results of the diagnoses. Protagonists of this point of view regard such a procedure as the destruction of the still totipotent cell for diagnostic purposes. Accordingly, they assert, the German Law on the Protection of Embryos would be violated by this method of diagnosis because it does not aim at the preservation of the embryo[82].

Holders of another view, who refer to the development in medicine and jurisprudence, especially in Anglo-American countries, raise objections against that. First and foremost they use the argument that PGD serves to avoid the possible need for a later termination of pregnancy for reasons of the so-called embryopathic indication or - as it is now dealt with in Germany - as a maternal indication.

The ethical legitimation of PGD is therefore derived from the being in a position to avoid a later termination of pregnancy. The extraction of a totipotent cell for biopsy also violates section 6 paragraph 1 of the German Law on the Protection of Embryos[83]. By extracting a totipotent cell, which is defined as an embryo[84] under German Law, a new Embryo comes into being showing genetic information identical to the remaining, original embryo. The current discussion in Germany also concerns the question of whether the extraction of blastomeres during the eight-cell-stage is permitted by law. In accordance with the present level of knowledge these cells are not totipotent any more, so that the restrictions contained in the German Law on the Protection of Embryos would not be

81 See also Diskussionsentwurf der Bundesärztekammer, DÄBl.2000, A-525.
82 Laufs, Die deutsche Rechtslage zur Präimplantationsdiagnostik, Ethik Med 1999, S. 55.
83 See also Günther in: Keller/Günther/Kaiser, Embryonenschutzgesetz, § 2 Rn. 54.
84 § 8 Abs. 1 ESchG.

applicable[85]. Nevertheless it is under consideration as to whether these tests with blastomeres during the eight-cell-stage violate section 2 paragraph 1 of the German Law on the Protection of Embryos, i.e. whether the tests in question are, or are not, designed for the preservation of the embryo.

In the latest discussions solutions compatible with the German Law on the Protection of Embryos have been put forward. These solutions are based on the medical tenet that a physician who extracts a cell from a human embryo is not allowed to influence the chance of the further development of this embryo negatively. This remaining embryo must still have the chance to be transferred to the womb. According to the latest opinions, this method can be referred to as a "neutral action"[86]. Though not being necessary to preserve the embryo, the test does not have a negative influence on its preservation, either. But consistent with section 2 paragraph 1 of the German Act on the Protection of Embryos it is required that the procedure be performed without the intention of protecting the embryo. The "crucial point" is that, arguing in terms of criminal law, the spirit of section 2 paragraph 1 of the German Law on the Protection of Embryos will never be fulfilled if one acts with the aim of protecting the embryo. Consequently one can go along with H. - L. Schreiber from Göttingen, who is a scholar and expert on medical law, that the tests are designed to ensure that there are no defects. From this argumentation one can conclude, that the pursued aim is primarily to protect the human embryo as a matter of priority. Consequently the tests do not constitute a violation of section 2 paragraph 1 of the German Law on the Protection of Embryos. Based on this argument one can conclude that preimplantation genetic diagnoses with cells that are not totipotent any more do not violate the German Law on the Protection of Embryos and therefore do not fall under German Criminal Law[87]. Of course the necessity of limitations in Criminal Law must be judged differently. This involves the need for wide discussion especially orientated to the Constitutional Law. The professional association of

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85 See also Neidert, Brauchen wir ein Fortpflanzungsmedizingesetz?, MedR 1998, S. 347, 353.
86 Günther in: Keller/Günther/Kaiser, Embryonenschutzgesetz, § 2 Rn. 56.
87 i. E. zust. Ratzel/Heinemann, Zulässigkeit der Präimplantationsdiagnostik nach Abschnitt D, IV Nr. 14 Satz 2 (Muster - Berufsordnung - Änderungsbedarf), MedR 1997, S. 540, 542.

German doctors (Federal Medical Association) is trying to make this decision easier by submitting a proposal for a PGD guideline[88]. The fact that the Association has not yet managed to formulate this guidelines shows how delicate the discussion is. It also shows, that even in regard to the etiquette of the bar it is necessary to have discussion among the social groups involved. So far, only a draft proposal for the guideline has been submitted. On the one hand, the professional association of German doctors requires a regulation that does not improperly limit the possibilities of modern PGD; on the other hand, the organisation emphasizes the need to protect human life. Paving the way for undesirable eugenics is especially feared. If the severity of a diagnosed disease were to be established in itself as a justification for aborting an embryo, it would result in a rift in society, because people who suffer from such diseases would then be stigmatized. This would be assessing the right of existence and the importance of an unborn human being in an ethically and legally unjustifiable way. In accordance with German regulations, there is only a small area, where prenatal tests are justifiable. Consequently, prenatal diagnoses in the form of PGD can only be indicated in individual cases, i.e. when, after qualified consultation, as prescribed by the Medical Association, it is demanded by the parents.

Embryo research is prohibited in Germany[89], but not in many other countries. That is the subject of Art. 18 of Bioethic-Convention[90].

Art. 18 paragraph 2 prohibits the production of human embryos for research purposes.

The research on embryos in vitro not produced for research purposes is not prohibited as long as the national legal system concerned provides adequate protection for embryos. The reason for this strict regulation is the following declaration of the Federal Constitutional Court, which also affects extra-corporal antenatal human life: ”Wherever human life exists,

88 printed in DÄBl. 2000, A-252.
89 See Deutsch, Medizinrecht, Rn. 440; Laufs, Fortpflanzungsmedizin und Arztrecht, 1992, S. 71, 78.
90 See the draft: BT-Drucks. 13/5435.

it shall be endowed with human dignity"[91]. " The German Law on the Protection of Embryos tries to enforce this not only by protecting those embryos which already exist but also by affording protection for those which are not yet even fathered."

This comprises 2 objectives: On the one hand, the creation of embryos that are already endangered from the moment of their fathering shall be prevented. On the other hand, genetic manipulation during the process of fathering shall be prevented since the risk cannot be calculated. And finally the significance of the human being in our legal order is varied[92]. But there is also the fundamental right to freedom of research. Freedom does not mean boundlessness. Freedom of research is restricted by other fundamental rights and constitutional goods[93], which is referred to as "competing constitutional law". Firstly, freedom of research is limited by the regulations of criminal law. Of course, freedom of research is also not applicable if an experiment contravenes a section of a Civil- or Criminal Code that protects constitutional goods. In Germany research on embryos for unspecified aims, is limited more strictly than in other countries. That is why there is a demand here for more freedom in line with what is already allowed abroad. But freedom of research is limited by other constitutional goods, especially the protection of human dignity, human life and human health. At first, the legislator has to formulate these constitutional limits in concrete terms. He will have to evaluate and balance the weighting of competing constitutional goods. The German Law on the Protection of Embryos already provides a concrete definition of these constitutional limits concerning work on and with embryos. The German Law on the Protection of Embryos and the jurisdiction of the Federal Constitutional Court originates from the protection of human dignity, that already takes effect from the moment of nucleus union[94].

The Federal Constitutional Court declared in its second judgement concerning the right of abortion dated 1993[95] and in the first decision dated

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91 BVerfGE 39, 1, 41.
92 See Laufs in: Laufs/Uhlenbruck, Handbuch des Arztrechts, § 129 Rn. 16.
93 BVerfGE 85. 360; Schmidt-Bleibtreu/Klein, Kommentar zum Grundgesetz, Art. 5 Rn. 17.
94 Hepp, Präimplantationsdiagnostik in der Diskussion, Frauenarzt 41 (2000), S. 832.
95 BVerfGE 88, 203.

1975[96], that already in the prenatal phase of life human dignity has to be protected. At the latest from the moment of nidation of the fertilized ovum in the uterus it is an individual, not divisible life. It already has a genetic identity. It is unique and distinctive. This develops while growing up as a human. The phases of the prenatal process of growing are indispensable as far as the development of an individual human is concerned. Therefore the human dignity of embryos is justified by their existence. The right of life is not only justified by the acceptance of the mother, but also by the existence of the embryo itself. It is an essential and inalienable right that is independent of religious or philosophical convictions[97]. The duty to protect the embryo, which is connected with the right to live, does not only refer to human life in general, but also to the individual life. The performance of this duty is an obligation of governmental authority.

This results in the prohibition of the unspecified use of human embryos and the cloning of human life[98]. The prohibition of cloning is connected with the prohibition of producing an embryo with the same genotype. These are reasons for restricting certain methods and results concerning work with pluripotent cells and tissues. The production of embryonic blasts from blastocysts is for different aims than safeguarding the embryo. This production is incompatible with the German Law on the Protection of Embryos even if the embryo remains undamaged. [99]

The taking of primordial germ cells from a dead foetus for scientific, therapeutical and diagnostic aims is regulated in the guideline for using foetal cells or foetal tissue. The guideline was compiled by the Federal Medical Association as a code of conduct. It is not contained in the German Law on the Protection of Embryos. It only regulates the period of time up to the nidation of the embryo in the uterus[100]. Transplantation Law is not applicable to embryonic and foetal organs and tissues. That means, taking primordial germ cells from a dead foetus is allowed under the currently

[96] BVerfGE 39, 1.
[97] Schmidt-Bleibtreu/Klein, Kommentar zum Grundgesetz, Art. 2 Rn. 20 b.
[98] See § 6 ESchG; Laufs/Uhlenbruck, Handbuch des Arztrechts, § 129 Rn. 21.
[99] See § 2 Abs. 1 ESchG.
[100] Günther in: Keller/Günther/Kaiser, Vor § 1, Rn. 2.

valid laws. This makes sense, because the situation is not comparable with that of an embryo since there are no totipotent cells involved. Nevertheless there are ethical problems. Regarding, for example, the consideration of parental rights and due respect for the dead. The medical use of the tissue of the aborted foetus for the posterior justification of abortion is the main danger. Because it is a matter of the production of human blasts in order to enable research on blasts, their production has to be restricted to a small number of cases.

The subject of preimplantational diagnostic processes and research on embryos involves very complex problems, which require profound discussion and to which there are no simple solutions. The characteristically cautious German approach, which is also referred to as ”the German malaise”, nevertheless has to be taken into account in connection with European co-ordination. It is to be feared but also expected that legal, regulatory measures will trail along behind the real situation. We must also address the question as to whether the danger of misuse must inevitably necessitate prohibition in the case of certain practices.

7. Moral Problems of Preimplantation Diagnostics

Günther Patzig

I have been asked to say something about the Moral Problems of Preimplantation Genetic Diagnostics ((PGD) in English and, mostly, (PID) in German.) Since I do not know enough about the discussion of the moral problems involved here in other European countries, I shall concentrate on the discussion in Germany, and, especially, on the literature I have listed.

It seems to me, that there has been less interest in the views of moral philosophers in this field in Germany than in other countries. Relatively few of our more prominent moral philosophers have been asked to take part in the deliberations on the different topics arising here. If you look, for instance, at the list of participants in the discussion of the working group of the Federal Medical Association ("Bundesärztekammer") which produced a well thought out discussion paper on guide lines concerning preimplantation diagnostics (See: Bundesärztekammer: Diskussionsentwurf) it contains the names of six professors of medicine, three professors of law, one professor of theology and one who is a member of an Institute for History and Ethics of Medicine; so that we may count him as half a philosopher. For Germany this is rather typical. In questions of ethics of science and medicine, theologians and jurists are regarded as authorities more than philosophers. There are reasons for this: philosophers have their individual, often idiosyncratic views, professors of law are representatives of what often is called the prevailing theory which is manifested in the courts' decisions, especially those of the German supreme courts respectively the constitutional court. Its rulings are regarded as possessing also a high moral authority. Theologians are representatives of the Protestant or Catholic Church and, therefore, also representatives of a large part of the German community.

On the other hand there are some professors of medicine, of law and of theology, who are also competent philosophers in their fields. But still

the discussion in bioethics in general and in the field of reproductive medicine especially, is, in Germany, more than elsewhere dominated by religious views and also by an attitude of almost unlimited respect for the law. That religious doctrine and the positive law and its interpretation by the courts may be legitimate objects of criticisms *on moral grounds* is a view which many, if not most people in Germany, find unappealing, to say the least.

In Germany the question of the acceptability of pre-implantation diagnostics became a matter of debate in September 1995, when Professors Diedrich and Schwinger applied to the Ethics-Committee of the medical university in Lübeck for a vote in the following case: A 27 - years old married woman had given birth to a child in 1990. It became evident that the child was suffering from Cystic fibrosis. The parents underwent genetic counselling and it turned out that they were both heterocygotic carriers of the recessive gene. So the chances of every prospective child to inherit the manifest illness were 25%. In 1992 and 1994 the woman became pregnant again; in both cases she underwent prenatal diagnosis, which found, in both cases, that the fetus was affected by the illness and she decided for abortion. In 1994 she learnt from newspaper reports that there was a chance of pre-implantation diagnosis and asked the director of the gynaecological hospital in Lübeck for help. The appeal to the ethics committee by the two professors was dated September 1995. In August 1996 the ethics committee of the Medical University decided, after careful deliberation (as documented in Düwell/Mieth, page 16 - 22), that there was no decisive *ethical* consideration against PGD in this particular case. But the committee could not rule out the possibility of a collision with § 1 number 1 of the "Law for the Protection of the Embryo" (1991), which expressly bans all experimentation with cells from an embryo in the phase of totipotency. Therefore, the committee advised the applicants to contact the government of the federal state (Schleswig-Holstein).

As far as I know the matter has not yet been settled; PGD is still, it appears, illegal in Germany. People in a situation comparable to the couple in question must try to seek help outside Germany, e.g. in Belgium or in England. (At the meeting in Bad Neuenahr I heard that the couple in

question went for PGD to Belgium; they are, in the meantime, happy parents of a healthy boy).

What are the factors at work that can explain this difference in attitude towards PGD and experimentation with embryos in general between Germany and other countries? 1. There may be several other factors involved, but two seem especially effective: The first is the "Sanctity of Life" doctrine which has led the constitutional court of West-Germany to decide that the guarantees for the right of life and human dignity must be effective from the moment of fertilization of the human ovum (Grundgesetz Artikel 1, Abs. 1, and Artikel 2, Abs. 2). There is no further requirement for the application of the fundamental rights of the constitution besides being a member of the human species and a human embryo even in its first days of existence belongs to that species without doubt.

Philosophers in general have become rather sceptical of such claim. Human dignity cannot, they tend to think, be based exclusively on membership in a biological species. To think like that would be "speciesism" which is as objectionable as racism or sexism. It was, of course, P. Singer, inventor of the term 'speciesism', who has insisted that not just by being *human*, but by being a *person* a human being has a right to guarantees of dignity and respect for his or her life. A human embryo is not a person but only a *potential*_person. Being a potential X, say being a potential king, or a potential Nobel prize winner, does not justify someone to expect being treated like an actual king or an actual Nobel prize winner; we would also not accept it if a potential terrorist would be treated as if he/she were already an active terrorist. One tends to think of Lichtenberg, the sage of Göttingen, who expressed his concern about Lavater's claims for physiognomy: "If physiognomy will deliver what Lavater expects from it, children will be hanged before they have committed the crimes for which the gallows would be just punishment".[101] Certainly, a potential king is somewhat different from ordinary persons and should be treated in a special way, and a potential criminal should also be treated with

[101] G. Chr. Lichtenberg, Schriften und Briefe, edited by W. Promies, München 1968, Bd. I, S. 532 Sudelbücher F 521).

special care. Accordingly, one should also deal with potential persons, even in their embryonic stage, with some special respect and care. But from this concession it does not yet follow that we must rule out unconditionally all experimentation with human embryos.

I think that the recommendations of the Warnock commission in England (1984) have defined a more reasonable solution of the problem: Human embryos should not be *produced* for research purposes; but those that have been produced e.g. for implantation after IVF and are redundant, may be used for (important) experiments until the 14th day of their existence. This would open the way for PGD.

One more word about our famous German Law on the Protection of Embryos ("Embryonenschutzgesetz") from the 1st of January 1991: It has often been described as one of the worst (formally and conceptually) laws that have been brought forward by our 'Bundestag', and that means much. In a rather mechanical way the law lists in its first seven paragraphs various types of activities in the field of IVF, genetic therapy and other ways of dealing with embryos, human ova or sperms and lists the corresponding punishments: "up to three years in prison or a fine", "up to five years or a fine". The *definition* of 'embryo' comes only in § 8 after seven paragraphs that state what punishment awaits people who do various things to embryos. Members of parliament who took a leading part in the public debate on "The Chances and Risks of Gene Technology"[102], have stated, in private, that the German Law on the Protection of Embryos of 1991 was the price the government parties had to pay for the consent of the critics of gene technology for projects that seemed - mainly for economical reasons - more important than genetic research on humans.

The debate therefore, whether such a law - and especially a law in this form - was really necessary is certainly not yet closed. In fact, in the current literature, almost ten years after the law has been passed, the thought of a new comprehensive law covering the whole field of reproductive

[102] Here I quote the title of the excellent report of the Catenhusen commission of the Bundestag, Frankfurt/M. 1987, 2nd edition 1990

medicine seems widely accepted[103]. The experience with the Law on the Protection of Embryos seems to show, however, that there are good arguments against all attempts to regulate in detail by law, and once for all such difficult matters which are also liable to be influenced by rapid changes in science and technology. This does not mean that the law must be adapted automatically from time to time to allow for technological advances. It means, however, that the law must not block progress which the law-giver could not consider at the time it was drawn up. A better policy, in my opinion, would be a statement of moral and juridical principles wide enough to cover new developments by competent application. This has been done successfully in German civil law since 1900; it is difficult to see why it could not also be done in the domain of the penal law. It is, by the way, remarkable that there has not been even, as far as I know, a single case brought before a court since 1991 on the basis of this law. This may be a sign that the penal law in general is not the best instrument to prevent developments in science and technology which are regarded as morally problematic or even outright dangerous.

Many authors in this field have also complained about striking inconsistencies and tensions in our overall law system. It has been said that the Law on the Protection of Embryos gives much stronger protection to the embryos in vitro than they would have in vivo. Their abortion (after the obligatory counselling session for the mother) is still, according to the revision of § 218a, Abs. I, StGB, "illegal but not liable to punishment". But in § 218a, Abs. II, we find that "Abortion is not illegal, if abortion is, according to medical judgement, required to avert danger to the life or the risk of a substantial impairment of somatic or psychic health of the pregnant woman, and if the danger cannot be averted in another way acceptable to her".

This is not at all satisfactory in a legal system which guarantees an absolute right of life to everyone, including embryos from the time of fertilization onwards. One might ask why this deference to the well-being of the pregnant women stops at birth of the child: What is the justification

[103] Cf. Schriftenverzeichnis, Nr. 6, page A 1221

for not accepting the killing of a new-born child or a small child later on, if the stress it causes to the mother is obviously seriously endangering her 'somatic or psychic health'? There must be a difference in the dignity and the right to life between a fetus and a born child, it seems, to explain the different attitude the law takes towards abortion and killing a born child. Incidentally, if the right of life guaranteed by our constitution in article 2 extends fully to the embryo from the moment of fertilization, why is abortion not regarded, consequently, as a case of homicide?

It seems then that in the German law system we have, on the one hand, a very marked emphasis on the protection of the right of life and the protection of human dignity extending even to embryos in the first stage of their development, which is inherently a difficult position to defend, and, on the other side, a readiness to accept the fact that the principle of protection of life from the time of conception onwards cannot be enforced in the matter of abortion, where public opinion seems to be strongly against any attempts of enforcement. This mixture of an ambitious idealism on the one hand and a 'realistic' opportunism on the other is, I think, rather dangerous in a legal system.

I now want to say something on the moral problems of PGD, without reference to the provisions of the relevant laws. This is a case in which a "topos" in Aristotle's technical sense becomes very prominent and important: I mean the so-called "slippery slope" argument, which, in Germany, is generally referred to under the name of the "Dammbruch" - argument. This metaphor uses the image of a flood pressing against a dam or dike and the necessity to keep the waters from finding a weak spot in the dam. For once the dike is broken in one place, the torrent of water will inevitably destroy the whole dike and cannot be kept back from inundating a large area of land. So, in the field of bioethics, we must be wary not to allow types of action or procedures that may on first sight look acceptable enough, but will gradually to a series of further developments, such that we cannot stop any more a progress to a scenario which we find horrible.

This type of argument is used frequently, but usually not in a rational way. In many areas it is used in the following form: An action A looks innocent enough. But if we accept or allow it, it is inevitable that action B, which is in some ways similar to A, will also become acceptable and common, and from here we get step by step to actions and situations of type N, which everyone would abhor. Therefore, to stop at the beginning this descent into hell we must - principiis obsta! - do all we can to keep people from accepting A. If we do not do this, later on there will be little chance to stop things from deteriorating further. A good example is the following, very popular argument in Germany: We should not allow a doctor to terminate the life of a patient who expressly wishes to die in view of a hopeless illness and intolerable suffering (A), because it is probable that some patients will ask for euthanasia not on their own free will, but under the influence, say, of their relatives (B). It will then be likely that doctors will terminate the life of their patients if they think that this is the best thing they can do for them even if the patients have not expressed a clear request for this (C). The next step would be that patients will be killed not only to spare them continuing hopeless suffering, but in view of the high costs and efforts implied in their nursing, especially in intensive care (D). And if we have reached this level of depravity, how could we hope to prevent a further development, at the end of which everyone who is old and ill and useless for the economy, will be eliminated even if he would prefer much to go on living (N)? And so we would be back by a few steps to the National Socialist ideas about euthanasia.

Now the important point about this type of argument is the following: It is not sufficient to imagine a scenario that might in this way come about. To give the argument of the slippery slope power it must also be shown that it is likely that the steps, one after another, will actually be taken, and, secondly, that there is not much of a chance to stop or even undo the harmful development once it has started. And that, in many, if not most cases, where the slippery slope argument is used, would be difficult enough to make plausible. I do not deny that there are cases where the slippery slope argument holds true but they are not that many.[104]

[104] I refer to the excellent study of Barbara Guckes: "Das Argument der Schiefen Ebene", Stuttgart 1997.

Now as to the danger of allowing Preimplantation Genetic Diagnostics to be put to practice: The dangers that have been brought up are: if PGD will become standard practice for IVF patients, other people that would have no difficulty to produce children in the normal way will, if they have some fears about genetic disabilities for their offspring, and find the prospect of abortion after prenatal diagnostics (PGD) too unpleasant, demand IVF plus PGD, because it is easier to decide in favour of non-implantation of an embryo than for abortion after 10 or 16 weeks of pregnancy. I do not think this will happen very often; if people must pay for the costly procedures, they will think twice about it. As a last resort one could make it illegal for people who do not need IVF to apply for PGD.

But those who have to use IVF might then insist that even if they have no special reasons for concern regarding genetic risks in their offspring, they would like to use the chance to make sure, and to be spared the discomfort (physical and emotional) of prenatal diagnosis with eventual abortion afterwards. This I do not think is a really bad thing. It might even be a compensation for couples that have to undergo the troubles of IVF, if they have a better chance than others to exclude grave genetic damage to the children in a less risky and troublesome way.

But people who have the genome of their future children tested will not demand that, as the potential of genetic diagnostics of at least monogenic illnesses enlarges, all possible genetic damage shall be ruled out, before they accept implantation of an embryo? Shall we not encourage the 'consumer-mentality' which makes people demand a "perfect child" to be delivered to them? I think that it would be possible to define a line between "negative" eugenics and "positive" eugenics and to rule out anything which comes near positive eugenics. The diagnosis should be limited to serious illnesses or handicaps like cystic fibrosis, thalassemia, sickle cell anaemia, Trisomy 21 and the like, which tend to make the child's life burdensome and, as a rule, short.

Most of the moral arguments against PGD are based on the debate on prenatal diagnosis (PND), and make use of the 'slippery slope topos'.[105]

[105] Cf. the contributions of Evelyne Gebhardt, Regine Kollek and Therese Neuer-Merbach in (3)

Besides the fear that PGD will step by step be extended and opened to prospective parents who have no particular genetic risks, just to make sure, and the fear of expansion of the kinds of genetic risks to be tested, there are also fears that the mentality in our society will become hostile towards handicapped people, that parents who would not on their own think of a genetic test like PND or PGD will be 'forced' by public opinion (so to speak: "voluntary coercion") to submit to such tests; there are reports that parents whose child is visibly a case of say, trisomy 21, were told by strangers "This kind of misery could have been prevented easily today" and the like.

There is also the argument that genetic selection will suggest to people who have the disease in question that "people like me ought not to exist".

As regards the hypothesis that people in general will become less "tolerant" (this term is actually used in the debate) against persons suffering from a genetic defect, there is no empirical evidence that there has been, on account of PND, a change in public attitudes towards people with a handicap. In Germany the institutional help for the handicapped has been considerably increased over the years; in general, the climate is in fact more friendly towards the handicapped than ever, which does not, of course, mean that conditions and provisions could not be improved. If we use PGD or PGD to reduce the incidence of genetic illness, there will in fact be more possible help for the individual cases which remain. We must also not forget that the cases of genetically caused disability and illness are only about 10% of all cases of disability in our society. So it would be strange if a reduction of the 10 % of the genetically disabled to say 2 % would change the attitude of the community towards disability in general.

One argument against preimplantation diagnosis, as against prenatal diagnosis, is probably more substantial. If we allow selection and abortion for embryos with a given symptom, persons who live with this might feel some insecurity concerning their own right of life. They might fear that 'a person like me should not exist' - according to general opinion. But understandable as this depressing idea is, it is certainly not rational. Many parents are not happy with the prospect of a baby at a time they find most

inconvenient. They may even think of abortion, but finally let things go their natural course. In most cases, they love their baby, once it is born. Should the child later on suffer from the idea that he or she was originally unwanted?

Even if our strange system of law declares embryos just after fertilization and grown-up people equally, as regards the right to life, protected, which, as I said, makes the § 218 a 1 StGB flatly unconstitutional, it is evident that there is a decisive difference between non-implantation of an embryo and even an early-term abortion on the one hand and killing a living, fully developed human being (with the exception of voluntary euthanasia in clearly defined cases) on the other.

Therefore, a person who has and lives with a disability or illness which is one of those looked for in pre-natal genetic tests, need not worry, and, therefore, the worries of disabled people cannot be used as a valid moral or legal argument against PGD.

In conclusion I want to refer to another problem which seems to be specifically German: As has been observed also by H. Hepp in (5) S.A. 1220, there is in the German law and in the bioethical discussion a kind of fear of contact concerning words and concepts as "selection" or "quality of life", "value of life" etc. This is, of course, quite understandable, even necessary: "Selection" is inevitably, by association, linked to the Terrors of Auschwitz; "value of life" reminds us of the title of the book by G. Binding und A. Hoche "Die Vernichtung lebensunwerten Lebens" of 1920, and of the T4-euthanasia programme from 1940.

Therefore, the StGB in its new version of the § 218 a 2 has dropped the "idiopathic" reason for a legal abortion: it is only the health of the mother which might be endangered by the prospect to give birth to a genetically disabled child that counts. It is politically incorrect in Germany to talk about difference in the "value of life" between individual persons. Now there is no denying that people think of their own life as more or less valuable and enjoyable, worth-while, and even the dreaded third-person view of the value of someone else's life - even the value of the life for society - is obvious. Would we not value the life of a mother of four child-

ren, a successful doctor or scientist or even a politician as more valuable to society, compared with the life of a dealer of drugs, a Mafia boss or a soccer hooligan?

The decisive difference from Nazi ideology is that value of life (either subjectively or objectively seen) can have no influence whatever as regards the right of life. Therefore, we should have no qualms to admit that in the case of grave genetic disabilities it is *also* our intention, in deciding for non-implantation, to spare a future child and person the necessity to spend a life with a handicap that may destroy all prospects to live if not happily, then even contentedly or tolerably unhappy. I do not see any moral objection to trying to improve the chances for a flourishing life of those about to be born.

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