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THE ETHICAL IMPLICATIONS OF RESEARCH INVOLVING HUMAN EMBRYOS

Final Study

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Abstract

Human embryo research is a well established feature of the modern scientific landscape. The technique has recently come to the fore in public policy debates because of new technological advances. Human embryo research now promises to play a pivotal role in the treatment of many chronic illnesses through developments in stem cell technology as well as continuing to offer hope for those who suffer from subfertility. Developments in the field of human stem cell research are, to a large degree, dependent upon human embryo research. There are conflicting pressures and arguments around this subject. On the one hand, there are those who argue that the need for therapies for diseases like Alzheimer's and Parkinson's is such in our ageing population that all avenues for research ought to be explored. These views are supported by those in the healthcare and pharmaceutical industries who have identified the tremendous potential for new treatments – and products. On the other hand there are those who argue that research upon human embryos violates fundamental moral norms and is an affront to the concept of human dignity. These divergent viewpoints are reflected in the existing and pending legislation among the member states of the European Union. Some states, such as the United Kingdom, have adopted a pragmatic and permissive approach to embryo research. Others, notably Austria and Germany, have established strong legal norms which reflect the moral argument that the human embryo has a status equivalent to any human being. Despite this apparently polarised situation there is much common ground to be found in the position of member states. This study examines the possible policy options for human embryo research in Europe. It analyses the existing legal positions among member states and provides a comparative assessment of policies adopted elsewhere, notably in North America. The study explores the ethical arguments relating to the fundamental questions of the moral status of the embryo. It also examines the recent public policy debates on the issues of human stem cell research and cloning.

Options Brief

This study has identified twelve possible policy options for action by the European Parliament in relation to the practice of human embryo research.

(i) **Prohibit research on human embryos.** Some European member states have enacted legislation which imposes severe restrictions on human embryo research. Others have adopted a much more permissive stance. A policy involving prohibition of human embryo research has the advantage of establishing a clear norm based on established, albeit contested, moral principles. Developing an appropriate regulatory mechanism to enforce a prohibition on such research may pose practical problems. The disadvantage of such a prohibition is that it could curb potentially beneficial research efforts. Such research will not necessarily be prevented *in toto* but will, in all probability, be displaced to other states.

(ii) **Prohibit the use of derivative medicines or products.** Even if embryo research is prohibited within the European Union there will still be a demand for the use of medicines or products which have been derived from such research. The European Parliament could attempt to prohibit the use of products or medicines derived from embryo research. Such a step would severely restrict therapeutic clinical applications based on such products. However, a prohibition on embryo research which permitted the use of derivative products may be difficult to defend.

(iii) **Prohibit some types of human embryo research.** States with a permissive approach to embryo research impose some restrictions on the types of research which can take place. Most prohibit practices such as reproductive cloning and the implantation of research embryos. The European Parliament could assemble an expert panel or group of advisors which could be tasked with categorising permissible and impermissible types of embryo research.

(iv) **Prohibit patents on products derived from human embryo research.** Directive 98/44/EC states that human embryos are to be considered unpatentable. This policy could also be extended to products and medicines derived from such research. Such a strategy would remove one of the major incentives for embryo research. It may, however, lead to the relocation of the research projects and may conflict with other recent strategies which seek to develop a European Research Area.

(v) **Restrict funding of human embryo research.** The European Parliament could attempt to prevent the use of EU funding for research projects involving the use, or destruction of, human embryos. This approach has been the subject of ongoing controversy in the United States and was attempted by the European Parliament in relation to Framework V in 1998. A ban on such funding carries strong practical and symbolic force. It would, however, restrict advances in research and may

lead to such research being conducted outside the European Union in states with less rigorous forms of ethical and scientific oversight.

(vi) **Restrict funding to certain types of embryo research.** The European Parliament could act, perhaps on the advice of an expert panel, to restrict funding to certain types of human embryo research. For example, projects involving cloning technology or embryo destruction could be excluded from research funding.

(vii) **Endorse the terms of the Bioethics Convention.** The European Convention on Bioethics is analagous to the ECHR but does not have a formal legal status within the European Union. The Convention contains internationally agreed norms on the practice of human embryo research.

(viii) **Impose a moratorium on certain types of embryo research.** The European Parliament could call for a moratorium on certain types of human embryo research. A moratorium could provide a useful interim step in advance of full risk assessments of controversial technologies. The difficulty with such a quasi-voluntary approach is that it may conflict with legislative positions already adopted by member states.

(ix) **Restrict the creation of supernumerary embryos.** Embryo research relies, primarily, on the use of donated supernumerary embryos. Legislation which limited the number of embryos created in each IVF treatment cycle could significantly impact upon the availability of embryos for research.

(x) **Restrict the cryopreservation of embryos.** The freezing of human embryos supports the practice of research. A policy which restricted the use of cryopreservation techniques would limit the extent of human embryo research. It would also have a negative impact on success rates in subfertility treatment.

(xi) **Create transnational norms based on consensus with the EU.** The European Parliament could seek to form policy based upon the existing consensus which exists between member states on issues such as time limits, cryopreservation and cloning.

(xii) **Create a regulatory authority.** Rapidly changing areas of scientific research can benefit from reflexive regulatory oversight. Such an approach permits ethical research to flourish without the need to develop rigid legal prohibitions which rapidly become outdated. It has the further advantage of sensitivity to changing ethical values and differing cultural contexts.

Executive Summary

Introduction

This Study was commissioned by the Committee on Industry, External Trade, Research and Energy. The Committee requested an informed assessment of current developments in the use of embryos in research and their ethical implications taking into account the regulatory environment. The Study considers the scientific objectives of human embryo research, the ethical issues which arise from such research and the legal context in which such research takes place.

The Science of Embryo Research

The practice of human embryo research has yielded significant benefits for sub-fertile couples. Over 300 000 children have been born using assisted reproduction techniques. Advances in human embryo research have also led to the development of techniques for preimplantation genetic diagnosis. Embryo research can now be utilised to benefit third parties through advances in embryonic stem cell technology. In 1998 two groups of researchers successfully isolated and cultured human embryonic stem cells. These cells are of particular scientific value because of their capacity for self-renewal and differentiation into a variety of cell types. Human embryonic stem cell research can be conducted using three methods:

- *Fetal tissue donation*. Germ cells can be removed from cadaveric fetal tissue.
- *Blastocyst derivation*. Stem cells can be isolated from the embryonic blastocyst.
- *Somatic cell nuclear transfer.* Cloning technology is used to create embryonic cells.

Human embryonic stem cell research has a number of possible therapeutic uses. The technology could be used to advance treatment in a number of chronic illnesses. Possible therapeutic uses of this type of embryo research would include:

- *Tissue Transplantation.* Cells from individual patients could be isolated, cloned and differentiated into tissue using SCNT techniques.
- *Cancer Therapy.* Embryonic cells could be used to reduce the effects of toxic cancer treatments.
- *Neurodegenerative Diseases.* Previously irreplacable nerve cells could be regrown using stem cell technology.
- *Bone Diseases.* Embryonic stem cells could be transplanted into patients to correct genetic disorders or to repair damage from trauma.
- *Blood Disorders.* Embryonic stem cells could be used to effectively treat diseases such as sickle cell anaemia.
- *Drug Toxicity Testing.* Embryonic cells could be grown in culture and used for toxicity testing in place of human subjects in clinical trials.

- *Organ Transplantation.* Animal models indicate that directed stem cells can be used to produce fully functioning organs for transplantation.

Ethical Concerns in Human Embryo Research

There are, however, serious ethical concerns which relate to embryonic stem cell research. There are four possible sources of human embryonic cells which could be used in furtherance of this type of research. Each raises ethical questions. The use of cadaveric fetal tissue as a source of embryonic cells raises the issue of complicity in the abortion process. The use of supernumerary embryos raises difficulties because the process of derivation of the stem cells necessitates the destruction of the embryo. The possibility of creating embryos purely for the purpose of research can be objected to on the deontological ground that it involves using the embryo purely as a means to an end. The use of cloning technology to create embryonic cells for research also generates social and ethical concerns.

The Moral Status of the Embryo

The moral status of the human embryo is a much contested issue. There are a spectrum of views on the subject. The argument that the human embryo is morally equivalent to an adult human being represents one end of this spectrum. At the other extreme is the view that the human embryo is little more than a commodity which can be subjected to any scientific procedure. Public policy in European member states tends, with some notable exceptions, to take an intermediate stance somewhere between these two polarities. Many states have established regulation based on the argument that the human embryo gradually acquires moral status as it develops. Such an approach facilitates research on embryos in the early stages of development. A number of states have adopted a fourteen day time limit for embryo research. This time limit reflects the point at which the primitive streak appears in the embryonic organism. If public policy rejects the argument that an embryo has full moral status and ought, therefore, to be protected from research, a limitation mechanism will be necessary to regulate the practice of embryo research.

Embryo Research Regulation: Canada and the USA

In 1996 the Canadian government enacted a comprehensive policy on the management of reproductive technology. The policy involved three components: a moratorium, a statute and a regulatory regime. The legislation explicitly prohibited thirteen particular types of research. A licensing system was established to monitor standards in research involving reproductive materials.

In the United States, human embryo research carried out using public monies is subject to extremely restrictive regulations. Similar research carried out in the private sector is not, in most states, regulated at all. In 1998 President Clinton asked the National Bioethics Advisory Committee to consider the issue of funding embryo research in light of the developments in stem cell research. The Committee report recommended that:

- Federal funding should be restricted to the use of cadaveric fetal tissue and supernumerary embryos;
- Federal funding should not be available for research involving the derivation or use of embryonic stem cells created purely for research;
- Federal funding should not be available for research involving cloned embryos;
- Donors of supernumerary embryos for research should be provided with adequate information to ensure informed and voluntary choices;
- Embryos and fetal cadaveric tissues should not be bought and sold.

Subsequent to this report the General Counsel of the US Department of Health advised the Director of the National Institutes of Health that funding research on pluripotent human cells did not violate the federal ban on embryo research.

Embryo Research Regulation: EU Countries

The regulation of embryo research in Europe reflects the diverging standpoints on the moral and ethical questions. A number of states have yet to enact explicit legislation on the issue.

Austria. Embryo research is regulated by the 1992 Act on Procreative Medicine. The central principle of this legislation is that reproductive medicine is only permissible within a stable heterosexual relationship for the purposes of procreation. Embryo research is prohibited.

Denmark. Law No. 460 of June 1997 regulates artificial fertilisation in connection with treatment, diagnosis and research. Article 25 explicitly refers to embryo research. It states that embryo research can only take place where the purpose is to improve *in vitro* fertilisation techniques or to improve techniques of preimplantation diagnosis.

Finland. The Medical Research Act 1999 addresses the issue of embryo research. The Act established a 14 day time limit for such research. The consent of the progenitors must be obtained prior to any research. The Act prohibits the creation of embryos purely for the purposes of research.

France. Loi No. 94-654 and subsequent relevant amendments restricts the use of reproductive technology to cases where the aim is procreative. Research can only be carried out where it offers a direct benefit to the embryo or where it would contribute to the improvement of reproductive medicine.

Germany. The 1992 Embryo Protection Act is a criminal statute which threatens up to five years imprisonment for those who breach its provisions. The law prohibits all forms of consumptive research on human embryos. It is an offence to attempt to fertilise an egg for any purpose other than bringing about a pregnancy.

Greece. Embryo research falls under the terms of the General Council for Health Statement of 1988. It states that embryo research is permitted until 14 days post-conception with the approval of the appropriate ethics committee.

Spain. The 1988 Law on Techniques of Assisted Reproduction states that research can take place with the progenitors consent in the first fourteen days. The research must be either applied research of a diagnostic character or must have a therapeutic purpose. Non-therapeutic research can only be performed on non-viable embryos.

United Kingdom. The Human Fertilisation and Embryology Act 1990 created a reflexive regulatory authority tasked with licencing the practice of embryo research. Licences will only be issued for research conducted before the appearance of the primitive streak at 14 days.

Transnational Regulation of Embryo Research

European Convention on Human Rights and Biomedicine. This Convention was signed by more than 30 participating nations in 1996. It is an analogous document to the European Convention on Human Rights which forms part of the general principles of European Union law. It explicitly states in Article 18 that where the law allows research on embryos it shall ensure adequate protection for the embryo. It also states that the creations of embryos for research purposes is expressly prohibited. In 1998 the Council of Europe approved a Protocol to the Bioethics Convention addressing the issue of cloning.

UNESCO Declaration. In 1996 UNESCO issued a Declaration on the Human Genome and Human Rights. The Declaration does not mention the human embryo explicitly but contains numerous articles reinforcing the need for respect for human dignity in research.

WHO Resolution. The WHO passed a resolution at the 51st Assembly which stated that the practice of reproductive cloning was ethically unacceptable and contrary to human dignity. The issue of non-reproductive cloning was kept under review. The 52nd Assembly noted that major clinical therapeutic benefits may come from the development of cloning techniques.

Embryo Research Regulation: European Union

There are a significant number of European Union norms which impact upon the issue of human embryo research. The European Parliament has passed three relevant resolutions. The 1989 Resolution on Genetic Engineering states that the human zygote needs protection and must not be subjected to arbitrary experimentation. The Resolution on IVF was also passed in 1989. It restricts the number of embryos which can be implanted

and calls for a ban on *ex vivo* genetic experimentation. In 1997 the Parliament passed the Resolution on Cloning which provides that cloning cannot under any circumstances be justified or tolerated by any society.

Directive 98/44 also addresses the cloning issue and states that patents cannot be granted for processes that involve human cloning. Decision 182/99 states that research activities which are conducted pursuant to the Fifth Framework programme must be carried out in accordance with fundamental ethical principles.

In 1997 the Group of Advisors on Ethical Issues in Biotechnology considered the question of cloning. The Group concluded that reproductive cloning was ethically unacceptable. It also noted that in those member states where non-therapeutic embryo research was permitted, research projects involving cloning could be permitted where the objective was to alleviate suffering or to provide insights into disease.

In 1998 the European Group on Ethics in Science and Technology issued an Opinion on human embryo research. The EGE was asked to address the question of EU funding of embryo research. The Group concluded that funding should not *a priori* be excluded but should be granted under strict conditions.

Part A: Options

A.1. Policy Options

There are a spectrum of possible policy options for the European Parliament in the area of human embryo research. These range from taking no active intervention on the issue through to efforts to prohibit the practice at the transnational level. The European Parliament can opt to take no immediate action and can await the creation of national norms in individual member states. Currently, Belgium, Italy, the Netherlands and Portugal are considering draft legislation. There is, however, a significant degree of overlapping consensus within the legislation which has, thus far, been enacted. A summary of the possible policy options include:

(i) prohibiting research on human embryos
(ii) prohibiting the use of medicines or products derived from human embryo research
(iii) prohibiting some types of research on human embryos
(iv) prohibiting the issuing of patents on medicines, products or procedures derived from human embryo research
(v) prohibiting the funding of research on human embryos
(vi) prohibiting the funding of certain categories of research on human embryos
(vii) formally adopting the norms of the Council of Europe Convention on Bioethics
(viii) imposing a moratorium on certain categories of human embryo research
(ix) restricting the creation of supernumerary human embryos
(x) restricting the cryopreservation of human embryos
(xi) reflecting an overlapping consensus of the national norms thus far adopted on human embryo research
(xii) creating a transnational body licensing embryo research.

A.1.1. Prohibit human embryo research

There have been calls already within the European Parliament for a prohibition on human embryo research. One attraction of this policy option is that it establishes a clear deontological norm. Such an approach has been adopted in Germany which has the very restrictive legislation on human embryo research. The exact mechanism by which a legal prohibition may be imposed could cause some difficulty. The German *Embryonenschutzgesetz*, for example, is a criminal sanction. In order to be truly effective at the European level a similar approach would have to be adopted. There is an obvious jurisdictional difficulty in terms of the competence of the European Union to impose criminal norms upon member states. An alternative approach could be the use of a regulatory mechanism which seeks to impose severe financial penalties on a country, institution or individual engaged in embryo research. There are also a range of arguments against engaging in a strongly prohibitive policy on human embryo research. If the European Union opposes embryo research it may succeed in preventing such research taking place in the European Union but it will not prevent it taking place

elsewhere. In such a scenario, scientific advances based on human embryo research will occur elsewhere. These will inevitably feed into the clinical practices which do take place in the European Union.

A.1.2. Prohibit the use of derivative medicines or products.

In the United States the NBAC report identified a difficulty in that, despite a prohibition on federal funding of embryo research, publicly financed research institutes were still seeking to use techniques and products derived from human embryo research which was privately funded. One response to this difficulty, which has also been noted in Germany, is to prohibit not only the practice of human embryo research but also the use of any derivative cell lines, products or techniques. A variation on this approach can be seen in the Biotechnological Inventions Directive 98/44 which prohibits the patenting of some medical procedures. The obvious problem with this strategy is that advances in human embryo research are likely to bring significant therapeutic benefits **(Part B 2.3.3.)**. A prohibition of the type suggested here is likely to restrict severely the clinical application of these medical advances. On the other hand, adopting a prohibition on embryo research, but allowing the use of derivative products, may appear to involve the operation of a double standard.

A.1.3. Prohibit some types of human embryo research.

A significant number of EU member states have enacted legislation permitting human embryo research subject to certain restrictions. One model might, for example, be that adopted by the United States National Institutes of Health Human Embryo Research Panel (HERP). The HERP outlined three categories of human embryo research: those techniques that clearly were acceptable, those that required additional scientific and ethical review and those that were definitely unacceptable. In the latter category the HERP included: cloning, research beyond the date where the neural tube closes, preimplantation genetic diagnosis for the purposes of sex selection, development of chimeras, cross species fertilisation, parthenogenesis and the implantation of human embryos. The HERP report pre-dates the developments in human embryonic stem cell research. In the European context, the contents of such a prohibitive list could be assembled by an expert panel or group of advisors. Such a strategy may reflect the norms which already exist in member states. Even in states with an apparently permissive approach to embryo research there are clear areas where research is not permitted. In the United Kingdom, for example, in addition to the 14 day time limit, research is not permitted on cloning for reproductive purposes. States with a restrictive regulatory system on human embryo research would be able to maintain their national legislation as the prohibited practices will already be covered by the restrictive national norms.

A.1.4. Prohibit patents on products derived from human embryo research.

Those engaged in human embryo research in the European Union are likely to seek to secure intellectual property rights for their endeavours through the acquisition of patents

on any new techniques or therapies developed. However, Directive 98/44/EC of 6th July 1988 states in Article 6(2) "…shall be considered unpatentable:…uses of human embryos for industrial or commercial purposes." In the European Union patents cannot, therefore, be acquired on the use of human embryos. **(Part B.7.2.1)**. It remains something of an open question as to whether derivative techniques, cell lines or treatments will also be considered unpatentable under Directive 98/44/EC. This ambiguity could be resolved by a policy which involved an explicit prohibition on the issuing of patents on medicines, products or procedures derived from or developed by human embryo research. Such a policy would inevitably alter the pattern of research in this area. It may also conflict with certain aspects of the recent policy on developing a European Research Area.

A.1.5. Restrict funding of human embryo research.

In September 1998 amendment No.36 was tabled by the European Parliament which sought to exclude from EU funding research projects which resulted in the destruction of human embryos. This amendment was directed at the 5th Framework Programme of the European Community for Research, Technological Development and Demonstration Activities. The European Commission sought an opinion on human embryo research from the European Group on Ethics in Science and New Technologies (EGE). The prohibition on public funding for human embryo research remains a policy option for the European Parliament. **(Part B.7.3.1).** This approach has also been followed in the United States where a prohibition on federal funding of human embryo research has been in place since 1979.

In 1994, in the United States, the HERP recommended that federal funding be approved for certain types of human embryo research. President Clinton immediately overruled the recommendation that human embryos could be created for research purposes. The NBAC revisited the issue of federal funding of embryo research in their recent report on the ethics of human stem cell research. **(Part B.4.2.)**. A prohibition on funding of embryo research in the European Union would clearly have an impact on the practice of embryo research. In the socialised European health care systems much basic and clinical embryo research relies on public sector funding. Such a prohibition would also carry a strong symbolic force by expressing a lack of ethical acceptance of the practice of human embryo research. A policy prohibiting EU funding for embryo research projects is subject to a number of criticisms. First, there is the obvious argument that a prohibition of EU funding will prevent advances in scientific research. Secondly, a prohibition on public funding will not prevent human embryo research but will simply see it either transferred out of the European Union or conducted in the private sector. Thirdly, private sector research or research conducted outside Europe will not be subject to the same degree of ethical scrutiny or oversight as that conducted in the public sector. Fourthly, it can be argued that while a non-funding policy will prevent embryo research there will be strong societal demand for therapies and pharmaceutical products derived from this research.

A.1.6. Restrict funding of certain types of human embryo research.

An outright prohibition on funding of embryo research has already been considered and explored by the EGE. This body issued an opinion in 1998 which stated that the 5th Framework Programme :

> "should not *a priori* exclude human embryo research which is the object of difficult ethical choices in different countries."

The opinion went on to suggest that particular concerns arose in relation to stem cell research. **(Part B.7.4.2.)** A policy could be devised so that public funding is not made available for controversial areas of research such as cloning and stem cell development. Alternately, research involving embryos which had been created solely for the purpose of experimentation could be prohibited. This accords with prohibitions contained in the legislation of a number of member states.

A.1.7. Endorse the terms of the Bioethics Convention

The Council of Europe Convention on Bioethics and Biomedicine has been signed by over 41 countries and international bodies. **(Part B.6.1.)** The Convention is legally analagous to the European Convention on Human Rights. While fundamental human rights have been considered to be enshrined in the general principles of European Community law, the ECHR does not have a formal legal status within the European Union. The Maastricht Treaty does state that "the Union shall respect fundamental rights, as guaranteed by the European Convention on Human Rights and Fundamental Freedoms….as general principles of Community law." However, this article appears in Title 1 of the Treaty and so is not enforceable by the ECJ. Nevertheless, human rights protection remains an objective in terms of Common Foreign and Security Policy. A similar approach could be adopted to the Convention on Bioethics given that the emerging difficulties of bioethics pose challenges for the European Union which are as severe as those raised by human rights abuses. Two sections of the Bioethics Convention are of particular relevance to the issue of human embryo research. Article 18 states that:

> "1. Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo.
> 2. The creation of human embryos for research purposes is prohibited."

The first clause reflects the fact that there was serious disagreement among the participating nations on the issue of embryo research. The United Kingdom, for example, derogated from the second clause as it conflicts with the terms of their national legislation on embryo research. The second aspect of the Bioethics Convention which is of relevance to the human embryo research debate is the Protocol on Human Cloning which was added in 1998. Article 1 of the Protocol states that:

> "1. Any intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited."

Cloning technology offers one possible source of embryonic cells for research. This clause of the Bioethics Convention would prohibit the development of such practices. The completion of the Bioethics Convention took almost a decade because of fundamental disagreements among participating nations. It has not been signed by some

of the member states. Formally endorsing the terms of the Convention may, therefore, prove to be controversial.

A.1.8. Impose a moratorium on some types of human embryo research

The European Parliament could call for an international moratorium on certain categories of human embryo research. This approach was, for example, adopted in Canada as part of a general policy initiative on reproductive technology. **(Part B.4.1.)** Moratoria have also been widely used in Europe in recent years in response to widespread concerns about the use of genetic testing in the formation of insurance contracts. The use of a moratorium is essentially an interim step which can be implemented to prevent certain practices while a more comprehensive legislative scheme is developed or until a full risk assessment can be performed. The difficulty with this approach in the European context is that there is already a variable approach to human embryo research among member states. An effective moratorium could only apply to those techniques which have not yet been fully developed. Moratoria are also limited in the sense that they are essentially voluntary measures which are not supported by the threat of strong sanctions.

A.1.9. Restrict the creation of supernumerary human embryos

Currently the most abundant source of human embryos for research comes from supernumerary embryos from IVF programmes. In order to increase the efficiency of the IVF technique clinicians in many countries tend to create more embryos than can actually be implanted *in utero*. These supernumerary embryos can either be destroyed, frozen or donated for research. **(Part B.2.3.2.2.)** If the number of embryos created were restricted to those which could be implanted then the scope for research on human embryos would be dramatically reduced. Only embryos which were specifically created for research purposes or created by cloning would be available for research. Both of these practices are prohibited by many member states with otherwise liberal regulation. One consequence of restrictions on the creation of supernumerary embryos is that the success rates for IVF treatment would be reduced. In Germany, no embryos can be created which are not intended for implantation. In Ireland, any supernumerary embryos created are transferred to the cervix of the woman, where they are expected to perish. A restriction on the creation of supernumerary embryos would also preclude the use of preimplantation genetic diagnosis which can be used to screen out certain genetic diseases.

A.1.10. Restrict the cryopreservation of human embryos

A similar strategy involves restrictions on the cryopreservation of embryos. The freezing of human embryos raises ethical and legal dilemmas. **(Part C.5.0).** Cryopreserved embryos can become the focus of custody or property law disputes if the progenitors disagree about their fate. The practice of cryopreservation is permitted in a number of European states. The time limits on the process varies. In Austria the limit is one year, in France the embryos can be frozen for up to five years with annual renewal of consent, while in Finland embryos can be cryogenically preserved for up to 15 years. The practice

of cryopreservation provides another ready source of embryos for research. A policy which restricted the use of freezing techniques on human embryos would reduce the scope for research. It would also reduce the success rates for IVF procedures and require women engaged in such fertility treatment to retrieve ova using laparoscopy procedures.

A.1.11. Create transnational norms based on consensus in the EU.

The European Parliament could seek to encourage the formation of a transnational norm on human embryo research based on the overlapping consensus which exists between a number of member states. The EGE identified this core area of agreement in their 1998 opinion on embryo research. **(Part B.7.4.2.)** They noted a number of areas of core agreement, including:

- 14 day time limit on embryo research
- prohibition on genetic modification of preimplantation embryos
- prohibition on the creation of animal-human hybrids
- prohibition on *in utero* transfer of research embryos
- need for progenitors consent to embryo creation

A number of other points could be added to this list. For example, there seems to be a degree of consensus that cryopreservation should be contingent on progenitor consent and should be time-limited. Similarly, there seems to be agreement that reproductive cloning should be prohibited. The European Parliament could seek to introduce these transnational norms by a number of methods. One obvious strategy would be to seek to include such specific restrictions in any future Framework Programme on research. Specific restrictions which reflect existing national norms in member states would not be subject to the types of criticisms contained in the EGE opinion on embryo research.

A.1.12. Create a transnational regulatory authority

Article 7 of Decision 182/1999/EC concerning the 5th Framework Programme states that:

> "All research activities conducted pursuant to the fifth framework programme shall be carried out in compliance with fundamental ethical principles."

The EGE opinion of 1998 recommended "systematic ethical evaluation, at Community level, of protocols of research on human embryos presented for Community funding." There seem to be few, if any, existing structures within the EU to facilitate such a systematic ethical evaluation. The rapidly changing nature of this type of research can benefit from a reflexive system of regulation. Such a system exists in the United Kingdom where licences for research projects must be approved by the Human Fertilisation and Embryology Authority. The advantage of such a method is that it permits ethical research to flourish without the need to establish strong statutory norms which may operate restrictively or quickly become outdated. A regulatory authority could also demonstrate sensitivity to the fundamental ethical principles which apply in the different member states. Such a system could ensure that ethical embryo research can take place within the boundaries of the European Union but that states which have a

strong ethical objection to such practices will not have a liberal system of regulation imposed upon them.

Part B: Arguments and Evidence

B.1. Introduction

This section of the study outlines background information, arguments and evidence to support the policy options which have been outlined in Part A. This part considers the science of embryo research, it surveys the major ethical arguments relating to embryo research and it presents information on the legal and policy background for such research.

B.2. The science of human embryo research

Research on human embryos has the potential to yield significant scientific advances. It also raises serious ethical and moral dilemmas. Embryo research has accompanied and, to a degree, accelerated advances in infertility treatment. Since the birth of the first test tube baby in 1978 more than 300 000 children have been born using assisted reproduction techniques. (Andrews, 1998). The initial promise of embryo research was the alleviation of symptoms of infertility. The process also led, in many cases, to the creation of supernumerary embryos which could be utilised in further research. Human embryo research is commonly conducted for the following purposes:

- To benefit the couple who provide the gametes
- To benefit the potential child
- To benefit a third party
- To increase general scientific understanding

In the early years *in vitro* fertilisation was, itself, seen as a research procedure and much of the experimentation was done to directly benefit the progenitors or the potential child. Advances in IVF have shifted the current focus of human embryo research to the development of embryonic cell lines and tissue or alternatively in basic scientific research which aims at enhancing the general corpus of scientific knowledge.

B.2.1. Preimplantation Genetic Diagnosis.

The first pregnancies established by the preimplantation genetic diagnosis (PGD) techniques took place in 1989. (Handyside, 1990). PGD can be used in aneuploidy screening for women of advanced age undergoing IVF or where male infertility is being treated following intra cytosplasmic sperm injection. PGD can also be used for the purposes of sex identification in order to avoid x-linked recessive diseases and to select out embryos which manifest indications of single gene defects. (Handyside, 1998).

The practice of preimplantation diagnosis involves removing ova from the woman using laparoscopy and fertilisation *ex vivo.* After fertilisation the one cell zygote begins to grow by cell division. At the eight cell stage, while all the cells are still pluripotent, a

single cell or blastomere is removed from the embryo. DNA is extracted from the cell and amplified using a polymerase chain reaction. The amplified DNA can then be screened against disease marker genes.(Handyside, 1992). The actual diagnosis of the biopsy cells is carried out using either flourescent in situ hybridisation (FISH) or polymerase chain reaction (PCR). The FISH technique can be used to detect chromosomal disorders. It is most commonly used to identify the sex of embryos in cases where there is a risk of an X-linked disorder. PCR can be used for the detection of single gene defects.

The disease-free embryos can then be implanted *in utero*. Blastomere biopsy and analysis raise some disturbing questions about the safety of such a procedure and the potential long term effects in children who are apparently "normal" at birth. (Norton, 1994). There are also concerns about the accuracy of the technique. Polymerase chain reaction is a complex process with substantial risks of contamination which can give a misleading result and may lead to a healthy embryo being discarded. While it is often argued that the preimplantation genetic testing technique raises fewer ethical issues than prenatal screening and termination the technique is not free from controversy.(Schubert-Lenhardt, 1996).

B.2.2.1. Practical Concerns in Preimplantation Genetic Diagnosis

Bonnicksen details a number of difficulties in relation to the practice.(Bonnicksen, 1992) First, there are safety concerns for the reimplanted embryos. The long term implications of blastomere removal remain unknown. Secondly, there are concerns about the accuracy of the procedure. All genetic diagnostic techniques have variable accuracy. The shortcomings can be due either to the technology used or to the variable expression of the disease itself. There is, therefore, in almost all cases, a fluctuating risk of false positive and false negative outcomes. The couple who choose the preimplantation technique because of personal objections to termination may find that their genetic diagnosis has been falsely negative and the fetus is affected in any case. Thirdly, the technique subjects pregnant women to some physical risk and the low success rate of the IVF procedure can cause psychological stress and strain. Fourthly, IVF technology is expensive and may take several cycles before a successful implantation takes place. Fifthly, the technique may be used for discriminatory practices, such as the selection of gender, (Jones, 1992) race (Berkowitz, 1998) or sexual orientation (Stein, 1998). Some of these issues have been addressed in the European context by the Group of Advisers on the Ethical Implications of Biotechnology which examined the ethics of prenatal diagnosis in 1995 and noted that:

> "the choice of sex or other characteristics for non-medical reasons is an ethically unacceptable indication for PND and should be prohibited." (GAEIB, 1995).

A recent consultation paper by the Human Fertilisation and Embryology Authority in the United Kingdom has listed the following difficulties with the practice of PGD. (HFEA, 1999).

- There is a possibility of misdiagnosis either due to a technical failure or because the biopsied material is not typical of the embryo.
- Embryos can become subject to mosaicism so that cells which appear similar under a microscope actually have a different genetic complement.
- Embryos may be damaged during the biopsy reducing the chances of successful embryo transfer.
- The long term effects of embryo biopsy are, as yet, unknown.
- PGD is dependent on the success of IVF. In the UK the live birth rate per treatment cycle is 17%. The figure for PGD will be lower than the general rate.
- PGD will be more expensive than IVF because of the complex molecular techniques involved in diagnosis.

B.2.2.2. Ethical Concerns in Preimplantation Genetic Diagnosis

Inevitably there are a range of views on the ethical acceptability of PGD. The Catholic theological position, set out in the *Donum Vitae* document in 1987, suggests that the creation of embryos is intrinsically immoral regardless of whether embryos have to be discarded in the process. In many countries it is argued that in order for *in vitro* fertilisation techniques to be commercially viable, more embryos than can ever be implanted have to be created. Under such practices surplus embryos will always be created and the scope for PGD will exist.

Glannon argues that the testing and selective reduction of genetically defective embryos is the only medically and morally defensible way to prevent the existence of people with severe disability, pain and suffering.(Glannon, 1998). He contends that beneficence requires that we not harm people by causing them to experience pain and suffering during their lifetimes. This leads him to the conclusion that there is a moral requirement to select and terminate embryos where the embryo has a disease-causing gene which will result in severe pain and suffering. Holland reviews four possible justifications for "differential treatment" of genetically based handicap.(Holland, 1998). The argument from genetic error is based on the notion that genes are sets of instructions, when those instructions are faulty, as is arguably the case with genetic disease, then we have the basis of an argument for treating that genetic error differently. A second argument is that based on parental responsibility. According to Steinbock and McClamrock, advocates of this view:

> "anyone willing to subject a child to a miserable life when this could be avoided would seem to fail to be living up to a minimal ideal of parenting."(Steinbock, 1994)

The argument rests on the duty of parents to refrain from procreation unless the potential child has the prospect of enjoying a good life. This reasoning might justify intervention to prevent the birth of children suffering from debilitating genetic diseases but it could equally justify similar intervention where the parents were poor or the relationship unstable. A third argument for differential treatment based on genetic disease is that based on the social consequences of the illness. This proposition seeks to justify

differential treatment where the potential child threatens to alter the lifestyle of the parents in an adverse way. Again Holland observes that such an approach could not just be restricted to those children likely to suffer from genetic disease. A fourth argument for differential treatment of those who potentially suffer a genetic anomaly is that it is better, where possible, to bring into the world a child without handicap. There are a number of problems with this view. One obvious hazard lies in the definition of handicap. Will a late onset genetic disorder such as Huntington's disease constitute a handicap? Similar difficulties arise in relation to the severity of the handicap in question. Huge variations in penetrance, expressivity and outcome are the norm in genetic disease.

Disabled rights groups advance a number of arguments against the use of preimplantation diagnosis for the purposes of selecting out genetically defective embryos. Buchanan analyses the various arguments put forward on behalf of the disabled. (Buchanan, 1996) One argument is characterised as the "loss of support" argument. In essence this is the claim that, since the use of genetic technology actually reduces the number of people suffering from genetically related disability, public support for those who do suffer from these disabilities will dwindle.

A second common objection to the use of preimplantation genetic testing by the disabled is the "expressivist argument." This is the claim that the use of genetic testing to attempt to reduce the amount of genetic disability expresses a judgment that the disabled are not full members of the community of human persons. Lindemann Nelson analyses the expressivist objection and explores the nature of the messages which can be sent by acts such as termination of genetically affected pregnancies. (Lindemann Nelson, 1998). He argues that reproductive decisions can be based on many and diverse motives. Some of those motives may signal disrespect for people with disabilities, but limiting the scope of women to engage in preimplantation diagnosis or other reproductive diagnostic techniques, will not, he argues, be the most effective means of challenging such disrespectful attitudes.

Buchanan develops a further argument in favour of preimplantation diagnosis based on justice. He argues that preimplantation genetic testing and the termination of genetically defective embryos can be morally required according to the principle of justice. In particular, his argument is based on the concept of equal opportunity and draws on the equal opportunity arguments developed by Rawls. (Buchanan, 1995.) Buchanan argues that an adequate theory of justice requires a commitment to equal opportunity. A commitment to equal opportunity requires not only the removal of legal barriers to opportunity but also the removal of more extreme disadvantages in initial social assets. This has generally been applied to the inequalities in educational and economic benefits that have been determined by the "lottery" of birth. Buchanan extends this sense of initial social assets to include genetic characteristics:

> "Thus, if one believes that there should be some limitations on at least the more extreme inequalities that arise through socioeconomic systems in which one's initial (undeserved, unchosen and unavoidable) social assets play a significant role in determining one's life prospects, then there is at

> least as strong a presumption that the same is true of serious disadvantages in natural assets."

Buchanan's conclusion is that justice, in particular equal opportunity theory, could require that preimplantation genetic testing be used to prevent the birth of children with debilitating genetic disease which could not be ameliorated through treatment after birth. Justice, according to Buchanan, requires societal intervention on both the genetic front and in changing the social and institutional infrastructure that create disability. His suggestion is that the use of genetic diagnostic techniques must be complemented with social policy measures based upon a concept of social solidarity.

B.2.2. In Vitro Fertilisation

The use of *in vitro* fertilisation as a treatment for infertility is now a well established component of modern reproductive medicine. However, those who hold the view that the human embryo has a moral status equivalent to that of adult human beings may find that they cannot support a technology that involves, in most cases, the creation of surplus embryos. Alternately, the fact that the "success" rates of the IVF procedure (in terms of successful pregnancy) remain well below 20% even in the most developed facilities has led some to question whether there are more cost-effective methods of remedying infertility. It has been argued that greater investment in understanding the causes of infertility would have a greater impact in the longer term than continued investment in IVF.

B.2.3. Human Embryonic Stem Cell Research

All mammalian tissues and organs derive from pluripotent embryonic stem cells which are present in the blastocyst in the early stages of embryonic development. In 1998 two groups of researchers successfully isolated and cultured human embryonic stem cells. These cells are potentially of great scientific interest because of their capacity for self-renewal and differentiation into a variety of cell types. Embryonic stem cells may offer a number of therapeutic benefits such as tissue and organ transplantation. They may also yield valuable information about embryogenesis, the mechanisms of abnormal development, human genetics and drug toxicity.

B.2.3.1. Methods of Human Embryonic Stem Cell Research

The particular ethical and legal challenges posed by the most recent innovations in human embryonic stem cell research arise from the fact that the research can only be pursued by using cells which have been derived from the destruction of embryos or fetuses. The cells can be developed from fetal tissue retrieved following an elective or spontaneous termination or from stem cells derived from the blastocyst of the early embryo. It may also be possible to use cloning technology to create embryos which can be used as stem cell sources.

B.2.3.1.1. Fetal Tissue Donation

The study by Gearhart *et al* involved isolating pluripotent human stem cells from fetal tissue. (Shamblott, 1998) The tissue was acquired from fetuses which had been terminated between five and nine weeks gestation. The donors of the fetuses had given informed consent to the use of the tissue after they had made the decision to terminate the pregnancy. The germ cells were removed from the area of the fetus which were destined to develop into the ovaries or the testes. These embryonic germ cells were then grown in culture.

B.2.3.1.2. Blastocyst Derivation

The research carried out by Thompson *et al* involved using a different technique for the derivation of embryonic stem cells. (Thompson, 1998). In this study pluripotent stem cells were isolated directly from the inner cell mass of human embryos at the blastocyst stage. The embryos used for the procedure were acquired from an infertility clinic. They had originally been created for reproductive rather than research purposes and were donated for research because they were in excess of the clinical needs of the donors. The isolation of the inner cell mass leads to the destruction of the embryo.

B.2.3.1.3. Somatic Cell Nuclear Transfer

A third possible technique for research into human embryonic stem cells involves the controversial method of somatic cell nuclear transfer. This technique is commonly known as cloning and issues related to it are discussed in detail below. The technical dimensions of the technique are discussed in Part C.

B.2.3.2. Ethical Issues in Human Embryonic Stem Cell Research

There are four possible sources for embryonic cells which could be used in stem cell research. These are:

- Embryonic germ cells derived from cadaveric fetal tissue
- Embryonic stem cells derived from supernumerary embryos
- Embryonic stem cells derived from embryos created for research purposes
- Embryonic stem cells derived from embryos created through SCNT

Each of these strategies for the creation of stem cells raises slightly different ethical issues.

B.2.3.2.1. EG Cells from Cadaveric Fetal Tissue

Cadaveric fetal tissue can provide a valuable source of fetal tissue which can be used for therapeutic purposes in transplantation or for research purposes. Embryonic germ cells taken from aborted fetuses offer one means of pursuing embryonic stem cell research.

Cadaveric fetal tissue tends to be taken from fetuses after elective terminations of pregnancy. In states where this practice is permitted detailed procedures have been constructed to ensure adequate consent and to insulate the decision to terminate the pregnancy from the research use of the tissue.

Those who support the use of cadaveric fetal tissue in human embryo research argue that, if abortion is considered to be acceptable, as is the case to some degree in most European states, then it must also be acceptable to use the fetal tissue for research. For those who find termination of pregnancy to be unacceptable it may still be possible to support this form of research by using tissue from non-elective terminations of pregnancy (miscarriage).

Opponents of this type of research claim that it can be seen as complicit with an immoral and unacceptable practice. It is argued that there could be a causal connection with, and even responsibility for, the decision to terminate a pregnancy that might otherwise have resulted in the birth of a healthy child. Alternately it has been argued that, even when safeguards protect against the possibility of a direct causal connection with termination, the research will be tainted through a symbolic association with unethical or immoral practices such as abortion. It is suggested that practices which claim to derive beneficial consequences from termination of pregnancy will gradually erode moral and political opposition to a highly contested practice.

B.2.3.2.2. ES Cells from Supernumerary Embryos

One obvious source of embryonic stem cells for research is from the extra embryos which are created in order to facilitate infertility treatment but which are not, for whatever reasons, finally implanted *in utero*. Large quantities of such embryos are created in modern clinical IVF practice. These supernumerary embryos can either be discarded immediately or, as is now common, can be cryopreserved for future use in either treatment or research. Proponents of this area of research argue that, since these supernumerary embryos will either be destroyed or frozen indefinitely, they ought to be used in beneficial scientific research projects. It is suggested that research upon these embryos is less ethically troubling than research using fetal cadaveric tissue because the embryonic development will not have progressed beyond the eight cell stage. Since, it is argued, the fate of these embryos is permanent storage or destruction, they should therefore be used to further scientific research.

Opponents of this type of embryo research point out that the practice of deriving embryonic stem cells from the blastocyst involves, of necessity, the destruction of the embryo. Those who argue that the embryo has an equivalent moral status to that of a human being can find this practice unacceptable. As fetal tissue, it has been argued that the progenitors may be influenced in their decisionmaking by the apparent beneficial possibilities opened up by the research. A further concern is that the embryo donors may seek to specify the type of research which their embryos are used for, or indeed, may seek to identify the recipients of the research. It is argued that the creation of supernumerary

embryos could occur deliberately in order to evade prohibitions on the specific practice of creating research embryos.

B.2.3.2.3. ES cells from Research Embryos.

One of the most ethically contested issues in relation to human embryo research is whether the creation of embryos purely for research purposes ought to be permitted. In the United Kingdom, the Human Fertilisation and Embryology Act permits this practice but most other European states do not. Advocates of a liberal approach to the creation of research embryos argue that the practice ought not to be prohibited because it is possible that advances in infertility treatment could mean that the availability of donated supernumerary embryos will be drastically reduced. If that occurs, it is argued, stem cell research programmes could be adversely affected. Furthermore, it is argued that certain types of embryonic stem cell research will require the specific creation of particular types of embryos. (Green, 1995). Such areas would include:

- *in vitro* oocyte maturation and oocyte freezing techniques
- research on the role of nutrition in early embryo development
- research on the effect of drugs on birth defects and childhood cancers.

Opponents of the creation of embryos for research adopt the Kantian argument that embryos should not be created merely to further the ends of scientific research. Even those who do accept that research can take place with donated supernumerary embryos may object to the practice of deliberately creating an entity for the purpose of engaging in destructive research. Many European states which have enacted legal norms on embryo research explicitly state that embryos which have been the subject of research cannot subsequently be implanted *in utero.* It has also been argued that prohibitions on the creation of embryos for research should be kept in place because there will be an adequate supply of donated embryos. Since stem cell lines are immortal the number of embryos needed to support the research in the first instance ought to be modest.

B.2.3.2.4 ES cells from Cloned Embryos

The use of SCNT technology to create cloned embryos has been proposed as a means of avoiding some of the ethical and legal restrictions on human embryonic stem cell research. The suggestion is that SCNT may not violate laws which prohibit the actual creation of human embryos because the use of this technique does not actually involve fertilisation. The technique uses the insertion of an entirely new nucleus from an adult cell into an enucleated oocyte. The attraction of this approach is that it sidesteps many of the ethical and moral concerns which surround the use of cadaveric fetal tissue, frozen embryos or embryos which have been created purely for the purpose of research. Proponents of this strategy note that many of the biosafety concerns about creating cloned human beings do not apply to this practice because the stem cells will be derived, and the embryo destroyed, at the blastocyst stage. It is argued that this type of research

could revolutionise organ and tissue transplantation by allowing patients to "grow" their own cell lines for transplantation purposes thereby avoiding tissue rejection problems.

Opponents of SCNT based embryonic stem cell research point out that the practice of cloning violates norms on human dignity. Many European states have signed the recent Council of Europe protocol on human cloning. At a national level the practice of cloning is frequently prohibited in national laws. In the United Kingdom the Human Fertilisation and Embryology Act apparently prohibits nuclear cloning in s.3.3(d) although a recent consultation paper has sought to make a distinction between reproductive cloning and therapeutic cloning. The recommendation was that the law ought to be altered in order to facilitate research into therapeutic cloning.

It has been argued that permitting "therapeutic" cloning could trigger slippery-slope style processes which might ultimately result in the acceptance of reproductive cloning. Those who oppose this practice argue that not all blastocysts may be destroyed in the stem cell derivation process. Embryos which survived beyond the eight cell stage may be placed at risk of disease if allowed to develop. Opponents also argue that if SCNT-based stem cell research were permitted it would divert research resources from other areas of research which could yield equally impressive results using less ethically troubling techniques.

Ethical Issues in Human Embryonic Stem Cell Research

Methods	Ethical Arguments For	Ethical Arguments Against
Embryo cells derived from cadaveric tissue.	• If abortion is considered to be acceptable then it is also morally acceptable to use the tissue derived from the aborted fetuses. • Those who find abortion morally unacceptable may still be prepared to accept the use of fetal tissue derived from spontaneous (non-elective) terminations.	• Causal responsibility for the termination of pregnancy. • Symbolic association with what are perceived to be immoral acts.
Embryo cells derived from supernumerary embryos.	• Modern IVF techniques inevitably generate supernumerary embryos. • These embryos can either be frozen, destroyed or donated for research. • Cryospreservation of embryos can create serious ethical and legal problems. • Since embryos will be destroyed in any event valuable scientific information could be obtained from using them in research. • Research takes place at an earlier stage of development than with aborted fetal tissue.	• Derivation of embryonic cells for research unavoidably causes destruction of the embryo. • Those who hold that embryo has equivalent moral status to human beings cannot accept this practice. • Decisions of progenitors may be influenced by the possibility of research. • Donors may seek to identify the recipient of the cells. • Donor may create extra embryos expressly for this purpose.
Embryo cells derived from embryos created purely for research purposes.	• The supply of supernumerary embryos donated for research may prove to be inadequate. • Some modes of research require the creation of particular embryos.	• Embryos will be created solely as a means to further the end of research. • There is little ethical, moral or social consensus on this practice in some states. • There may be an adequate supply of donated embryos.
Embryo cells derived from embryos created by SCNT. (cloning)	• This practice may not violate norms opposed to the creation of embryos because fertilisation is not taking place. • Avoids the problems of using cryopreserved embryos, donated embryos or those which have been created purely for research. • Biosafety concerns in relation to cloning do not apply because the cells will be derived at a very early stage. • Some states have stated that human cloning for therapeutic purposes is acceptable.	• Cloning violates norms on human dignity. • There may be risks to any cloned embryo which is not destroyed by the derivation of ES cells. • Cloning technology would divert resources from other needs.

B.2.3.3. Therapeutic Uses of Human Embryonic Stem Cell Research

Embryo research has clear implications for the development of therapeutic interventions. Embryonic stem cells could provide therapies for many of the most common diseases. Research involving human embryos offers the potential to develop treatments for neurological diseases such as Parkinson's and Alzheimer's, for chronic diseases such as coronary heart disease and for those which have a severe effect on quality of life such as diabetes. The Table below summarises out some of the major possibilities for such research.

The possible therapeutic uses of human embryo research

Possible Treatment	Detail
Organ Transplantation	Embryonic cells could be created through the use of somatic cell nuclear transfer techniques(SCNT). The patients own cells could be isolated and cloned thus avoiding tissue rejection problems.
Cancer Therapy	Embryonic cells could be used to reduce the effect of toxic cancer therapy. Similarly such cells could be used to revive the immune response of patients undergoing bone marrow transplant.
Neurodegenerative diseases	Most of these diseases arise through the loss of irreplaceable nerve cells. Fetal tissue transplantation in Parkinson's disease has slowed or stopped disease progression. Similar progress may be possible with diseases such as multiple sclerosis, Alzheimer's disease and Huntington's disease.
Bone/cartilage disease	Embryonic stem cells could be transplanted to an individual in order to treat genetic disorders related to bone and cartilage such as the chondroplaysias or osteo-arthritis.
Blood disorders	Stem cell transplantation may provide therapies for diseases such as sickle cell anaemia.
Drug toxicity testing	Embryonic cells could be cultured and used to test the efficacy and toxicity of certain drug products. This could obviate the need for the use of human subjects in clinical trials.
Transplantable organs	Research into directing the growth of embryonic stem cells may make it possible to grow transplantable organs.

B.2.3.3.1. Transplantation

Research involving human embryonic stem cells could lead to advances in those areas of medicine where therapy involves transplantation. One of the most likely uses of this technology in the near future is the treatment of type-1 diabetes through the transplantation of pancreatic islet cells or beta cells produced from autologous human pluripotent stem cells. These cells could reenter the pancreas and provide normal insulin production. In the longer term gene transfer into pluripotent stem cells could remove the

need for immunosuppressive drug regimes in organ transplantation. The use of stem cell technology may also offer new therapeutic strategems for autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus.

B.2.3.3.2. Cancer

Human pluripotent stem cell research may also yield advances in the cancer research and treatment. Stem cells could be used to treat the tissue toxicity which is induced in conventional cancer treatments such as chemotherapy and radiotherapy. Pluripotent stem cells may be able to return a full immune response to patients who are undergoing bone marrow transplantation. Research into the properties of human stem cells may also provide insights into the ability of cells to renew themselves. This may, in turn, help in the development of therapies aimed at preventing cancerous cells from replicating. Stem cell research could also assist in oncology research and practice by providing stem cells for gene therapy experimentation. This could facilitate the construction of cells which are resistant to chemotherapy.

B.2.3.3.3. Neurological Diseases.

In the United States, the National Institute of Neurological Disorders and Stroke has recently stated that:

> "in no area of medicine is the potential of stem cell research greater than in diseases of the nervous system."

The reason for this claim is that many diseases result from loss of, or deterioration of function in, nerve cells. One unique property of mature nerve cells is that they cannot divide to replace loss or damage. In Parkinson's disease, the nerve cells which make dopamine die. In Alzheimer's disease the cells that make acetylcholine die. In amyotrophic lateral sclerosis the motor cells which activate the muscles are lost. In all these cases the lost or damaged cells cannot be replaced. In cases of stroke, trauma or spinal cord injury significant loss of function follows the destruction of irreplaceable nerve cells. The promise of human stem cell research is that new nerve cells can be developed to replace those which have been lost and damaged. Work involving fetal tissue transplantation has already demonstrated the possibility of restoring function through cellular transplant. Ethical concerns and a shortage of donated fetal tissue have been limiting factors in this work. Stem cell research offers a means of providing large quantities of differentiated nerve cells.

B.2.3.3.4. Bone Diseases

Human stem cell research may lead to the generation of replacement cells and tissues to treat diseases of the bone and cartilage. The use of transplantation techniques could facilitate long-term correction of diseases or degenerative conditions where bone or cartilage cells are either deficient in number or defective in function. Similarly, an

individual's own stem cells could be genetically modified and reintroduced with the same effect. This approach offers possibilities for diseases such as osteogenesis imperfecta and the chondrodysplasias. Another application of the technology could involve the differentiation of stem cells into bone or cartilage producing cells. These could be introduced into damaged areas in instances of osteoarthritis, fracture or surgery.

B.2.3.3.5. Blood Disorders

Stem cell research may facilitate advances in the treatment of some common blood disorders such as sickle cell disease. The epsilon globin gene has been shown to block the sickling effect in sickle cell haemoglobin. Currently this gene is only expressed in embryonic red blood stem cells. Research in such embryonic stem cells could help to provide an understanding of how the epsilon gene could be switched on in adult blood cells.

B.2.3.3.6. Drug Toxicity

All pharmaceutical products require a rigorous programme of testing before release onto the market. The later stages of this process require toxicity testing in human clinical trials. These trials are expensive and raise grave ethical questions. Human stem cell research could allow the development of cheaper and more efficient toxicity trials on pharmaceutical products. Similarly, such research could allow a greater understanding of the effects of environmental toxins on embryonic and fetal tissue development.

B.2.3.3.7. Transplantable Organs

Recent research in animals has shown that it may be possible to generate entire transplantable organs from a tissue base. Such an approach would obviously overcome the problems of tissue rejection and shortage of donor organs in modern transplant programmes. A recent project has successfully grown bladders which have been transplanted into dogs and shown to be functional. (NIH, 1999).

B.3. Ethical Issues in Human Embryo Research

While the use of *in vitro* fertlisation technology may have become a mainstream component of modern obstetric practice, the use of human embryos remains an ethically controversial area. This section of the Study examines some of the ethical issues surrounding human embryo research.

B.3.1. The Definition of the Embryo

Many of the regulations and legislation which are currently in place refer explicitly to the human embryo. There is, however, a divergence of view as to the appropriate definition of a human embryo. In the United States the National Bioethics Advisory Commission adopted the following terminology:

- Zygote - the developing organism in the first week after fertilisation
- Embryo - the organism in the second to eighth weeks after fertilisation
- Fetus - the organism from the ninth week of development onwards

In Canada, the *Proceed with Care* report noted that, in biological terms, the word embryo refers to the developing entity after implantation in the uterus. Prior to implantation the appropriate biological term is zygote. Nevertheless, popular perception and usage tends to describe zygotes as embryos. The matter is further complicated by the use in some states, such as the United Kingdom, of the term "preembryo" in legislation. The Human Fertilisation and Embryology Act regulates *inter alia* experimentation prior to the emergence of the primitive streak. This occurs at 14 days post conception. Prior to this point the Act describes the entity as a "preembryo". Confusion can arise from this usage because, strictly speaking, the first fourteen days after fertilisation see a development from zygote to embryo, both of which are encompassed in the "prembryonic period." The resolution adopted by the NBAC in the United States was to continue to use the broad terms embryo research, embryo donation and embryo transfer to refer to zygotes. Some caution does, clearly, need to be exercised in the development of binding norms where these concepts are used. In 1989, the European Parliament passed a resolution calling for a clear definition of the human embryo in order to provide unequivocal protection for its genetic identity.

B.3.2. The Moral Status of the Embryo

The moral status of the human embryo has been the subject of much controversy and academic debate. There is a spectrum of possible positions which can be taken on the moral status of the embryo.

B.3.2.1. Full Personhood

At one pole of the spectrum is the view that the human embryo has a moral status equivalent to that of an adult human being from the moment of conception. This position is commonly associated with certain theological perspectives. (Doerflinger, 1999). The Roman Catholic Church, for example, in the 1987 *Donum Vitae* notes that:

> "The conclusions of science regarding the human embryo provide a valuable indication for discerning by the use of reason a personal presence at the moment of this first appearance of a human life: how could a human individual not be a human person?"

The use of IVF technology can be problematic for those who hold this moral point of view since the techniques carry an inherent risk that some of the embryos created will not be implanted and will be destroyed or used in scientific research.

The stem cell experiments which involve destruction of the human embryo clearly pose difficulties for those who adhere to this perspective. The pioneering work of Gearhart involved obtaining tissue from embryos/fetuses which were terminated between five and nine weeks gestation. (Shamblott, 1998). Embryonic stem cells can also be derived from preimplantation embryos which have been created using IVF technology. The stem cell research carried out by Thompson *et al* involved the development of supernumerary embryos to the blastocyst stage at which point they were dissected and the stem cells removed. (Thompson, 1998). The Catholic Magisterium holds that this form of research involves the destruction and degradation of human life and is, therefore, impermissible.

Those who hold this perspective on the status of the embryo will face a further problem as therapeutic interventions developed from stem cell research become more widespread. This raises the issue of moral complicity (Brannick, 1999). Pope John Paul II addressed this point explicitly in *Evangelium Vitae*:

> "Indeed, from the moral standpoint, it is never licit to cooperate formally in evil. Such co-operation ….can be defined as a direct participation in an act against innocent life or sharing in the immoral intention of the person committing it."

From this perspective it can be seen that those who hold the view that human life is entitled to full moral status from the moment of conception may be restrained by notions of complicity from engaging with the beneficial effects of human embryo research. Similar reasoning has been used to justify the rejection of useful research data accumulated by Nazi doctors. The issue of complicity was addressed in the United States recently where a federal ban on the funding of embryo research has been in place for some years. The director of the National Institutes of Health (NIH), Harold Varmus, announced that, notwithstanding the ban, research on cell lines derived from human embryos was not in violation of the federal ban. Some leading Catholic theologians reject this approach. Doerflinger, for example, argues that those who harvest and use embryonic stem cells are necessarily complicit in the destruction of the embryo. Such individuals take the cells from the embryos while they are still "living" and the method of destruction is determined entirely by the needs of the researcher. He argues that:

> "a government agency that funds such research is directly promoting the destruction of human embryonic life."(Doerflinger, 1999).

B.3.2.2. Gradual Moral Status

The view that the developing embryo acquires moral status as gestation proceeds has underpinned a number of policy statements on human embryo research. The Warnock Committee, which examined the matter in the United Kingdom, took the view that:

> "The human embryo… is not under the present law of the United Kingdom accorded the same status as a living child or adult, nor do we necessarily wish it to be accorded the same status. Nevertheless, we were agreed that the embryo of the human species ought to have a special status." (Warnock, 1984)

This notion of a special moral status falling somewhat short of that which is applied to human beings is also reflected in the US Department of Health, Education and Welfare Ethics Advisory Board study which noted that:

> "the human embyro is entitled to profound moral respect, but this respect does not necessarily encompass the full legal and moral rights attributed to persons." (Ethics Advisory Board, 1979).

Those who hold this perspective do not consider embryos to be commodities and therefore oppose the purchase or sale of embryos. They may also oppose the creation of embryos solely for research purposes such as embryonic stem cell research.

In policy terms, this argument has been influential in the adoption of legal time limits constraining embryo research. In the United Kingdom, the Human Fertilisation and Embryology Act allows embryo experimentation under licence up until the fourteenth day after fertilisation. The argument for a fourteen day limit was the emergence of the primitive streak. There are other alternative time limits which reflect the position that the human embryo gradually acquires moral status:

- 14 days - emergence of the primitive streak
- 18 days - beginning of neural tube development
- 22 days - onset of the fetal heartbeat

All of these time points reflect a linkage between a physiological change and the acquisition of some moral status. In the United States, the Human Embryo Research Panel also settled upon a fourteen day time limit for embryo research. The argument advanced was that:

> "formation of the primitive streak at around fourteen days of development and the beginning of cell differentiation and individual organization marks another stage of development that merits an enhanced degree of protectability." (NIH, 1994).

It has been argued that the reasoning adopted by bodies such as the HERP and the Warnock Committee reflects a political rather than a moral choice on the status of the embryo. Freeman argues that the choice of a fourteen day time limit is:

> "driven primarily by instrumental concerns and policy compromises, rather than any particular moral feature of the embryo. This point is important, because when contemplating research involving human subjects, intrumental rationales and arbitrary policy compromises that pass for moral justification should be scrutinized critically." (Freeman, 1996).

The primitive streak-based fourteen day limit is based on the criteria of individuation. After the emergence of the primitive streak, it is argued, the developing embryo can no

longer divide into more than one being. Twinning of the embryo or the aggregation of two or more cleavage-stage embryos are no longer possible. Once the primitive streak has appeared the cells of the inner cell mass begin to differentiate into specialised types of tissue. (Tauer,1997).

There are other possible criteria which could be applied and which could yield a different time limit for embryo research. Such criteria would include:

- genetic uniqueness
- potential for full development
- sentience
- brain activity
- degree of cognitive development
- human form
- capacity for survival
- relational presence to the mother

Each of these could be used to create a cut-off point for embryo research in states where the embryo is regarded as having a moral status somewhere between full personhood and commodity. In the United States the HERP rejected the "single criteria" approach to the moral status of the embryo and instead considered the cumulative effect of a number of the possible criteria in setting a 14 day limit on research.

B.3.2.3. Embryo as Property

At the extreme end of the spectrum is the position which holds that the human embryo has no specific moral status and ought to be treated as a commodity which is the property of the progenitors. Such a view affords the couple an absolute discretion over the fate of the embryo. Such a position is rarely expressed in any normative frameworks although some judicial rulings in the United States on the disposition of supernumerary embryos have moved close to ruling that embryos were the property of their creators. (Diamond, 1998). In the 1993 California Court of Appeals ruling in *Hecht* v. *Superior Court of Los Angeles County* acknowledged that "the present legal position towards property rights in the human body is unsettled" but that "frozen sperm is a unique type of property." In Australia, the matter of cryogenically preserved embryos has been considered in the 1996 case *In re Estate of the Late K*. The Supreme Court of Tasmania held that a frozen embryo possessed a contingent interest in the estates of its deceased progenitors, although that interest did not actualise until the child was born. The attraction of the property law approach to embryo status is that is affords a straightforward resolution based on mature legal principles. However, obvious difficulties arise in relation to disposition disputes. (see C.5.0).

B.3.3. The Use of Donor Embryos

Most current *in vitro* fertlisation practices result in the creation of supernumerary embryos. If these embryos are not implanted they will usually either be allowed to perish or be donated for research purposes. In the United Kingdom the law permits

experimentation or research on such embryos until the fourteenth day after conception or fertilisation. The Nuffield Council on Bioethics recently recommended that donor embryos be utilised for the purpose of generating and collecting embryonic stem cells. (Nuffield, 2000). In the United States, the Director of the National Institutes of Health issued draft guidelines on the use of human embryos for stem cell research in December 1999. (NIH, 1999). These guidelines outline a number of key restrictions on the use of donated human embryos. These include:

- no inducements, monetary or otherwise, should be offered for the use of donor embryos
- there should be a clear separation between the decision to create embryos for IVF treatment and the decision to donate supernumerary embryos
- individuals undergoing fertility treatment should only be approached about the donation of embryos at the time of deciding the disposition of supernumerary embryos
- donation of embryos should be made without any restriction regarding the recipients of cells derived from the pluripotent stem cells
- the donors should provide fully informed consent to the donation of the embryos for research involving derivation of stem cells.

Similar guidelines have been developed elsewhere to address concerns about fetal tissue transplantation.

B.3.4. The Creation of Research Embryos

The question of whether human embryos should be created purely for the purposes of research can be problematic even for those who are supportive of other forms of embryo research. Those who find the use of supernumerary embryos for research acceptable may still be opposed to the creation of embryos for research. As Robertson notes:

> "such individuals oppose the creation of research embryos either because of consequentialist concerns about the effect of such practices on other persons or because of deontologic or symbolic/constitutive concerns about showing respect for human life." (Robertson, 1999).

Opponents of the creation of research embryos argue that the practice could cheapen the act of procreation and lead to the commodification of embryos. It is also suggested that the process would put women at risk in a project which could provide them with no possible form of benefit. (Annas, 1996). Annas objects to the "manufactured-orphan" status which would accompany an embryo created purely for research:

> "The moral problem with making embryos for research is that as a society we do not want to see embryos treated as products or as mere objects, for fear that we will cheapen the value of parenting, risk commercializing procreation and trivialise the act of procreation." (Annas, 1996).

The recent Nuffield Council on Bioethics Report recommended that:

> "while there are sufficient and appropriate donated embryos from IVF treatments for use in research, we consider that there are no compelling reasons to allow additional embryos to be created merely to increase the

number of embryos available for ES cell research or therapy." (Nuffield, 2000).

Many of the arguments ranged against the creation of embryos for research purposes are consequentialist in nature. These arguments include the following:

- research embryos will be used for trivial purposes (e.g. toxicology studies)
- research embryos will be bought and sold on an open market
- the use of research embryos will undermine respect for other human research subjects
- the use of research embryos will cheapen or demean human reproduction and parenting
- the process may have a negative impact on the donors of oocytes.

There are also a number of deontological objections to the creation of embryos for the purposes of research these include:

- human embryos have an inherent moral status and their creation for research represents inherent disrespect for human life
- creating an embryo with the intention of not transferring it to a uterus treats the embryo as a mere means to an end
- human embryos act as a powerful symbol of human life and ought therefore to be protected.

In the United Kingdom, the passage of the Human Fertilisation and Embryology Act 1990 explicitly permitted the creation of human embryos for research. The legislation is structured so that the determining factor in approval or rejection of an embryo research project is the scientific objective rather than the mode of creation of the embryo. Research projects involving the creation of human embryos have been permitted for studies into advances in fertility treatment. Similarly, in the United States, the HERP report in 1994 recommended that embryos could be created solely for research purposes where:

(i) the research in question could not otherwise be validly conducted, and;
(ii) where it was necessary for the validity of a study of outstanding scientific and therapeutic value

These recommendations were not favourably received by the legislature which subsequently voted to ban federal funding of all embryo research regardless of the source of the embryos.

B.3.5. Creating Embryos by Cloning

The use of SCNT technology has been mooted as one means of avoiding some of the ethical difficulties surrounding the deliberate creation of embryos for the purpose of research. SCNT allows stem cell lines to be generated using somatic cells. This process offers potential benefits in tissue and organ transplantation as it allows autologous grafting with a reduction in the risk of rejection. There are, of course, major technical and ethical difficulties with such a process. The production of cell lines using SCNT would require a large quantity of donated human oocytes for the nuclear transfer

procedure. This may prove to be a major technical and ethical hurdle. Current availability of mature oocytes for donation is limited and suggestions have been made that bovine oocytes could be utilised to culture human embryonic stem cells. Such a practice would, of course, raise a new series of ethical questions. The Nuffield Council on Bioethics in their recent paper on the ethics of stem cell research nevertheless state that:

> "we consider that the proposed creation of embryos using SCNT for research into the derivation of stem cells offers such significant potential medical benefits that research for such purposes ought to be licensed."

The Council also recommended that the United Kingdom law should be amended in order to permit research involving embryos for the purpose of developing tissue therapies from derived ES cells.

B.3.5.1. Reasons for Reproductive Cloning

Human reproductive cloning is currently just beyond the boundaries of scientific possibility. Nevertheless arguments have been put forward by those who think that reproductive cloning ought to be used in some circumstances. (Andrews, 1998) Arguments for such a practice include:

- if one or both members of a couple are infertile cloning may be a viable reproductive option
- if one member of a couple has a genetic disorder has that they do not wish to pass on to any child then cloning the unaffected partner may be an option
- if both partners are found to be carriers of a recessive genetic disease and do not wish to run the risk of having an affected child then they may wish to clone
- parents may seek to clone a dying child

B.3.5.2. Risks in Reproductive Cloning

There are many risks inherent in cloning technology. The weight of these risk factors clearly increases when the technology is utilised for reproductive purposes. It is worth recalling that of the 277 attempts by the Roslin institute to clone a sheep, only one survived. The risks involved in reproductive cloning include:

- the process of cloning may damage the DNA in the cell leading to long term genetic abnormalities
- premature ageing due to the shortening of teleomeres in the cell
- cloned animals have tended to be abnormally large
- cloned animals have extremely high post-natal mortality
- loss of genetic diversity increases risks of disease

B.3.6. Embryo Research using Cadaveric Fetal Tissue

There is a linkage between the ethics of using cadaveric fetal tissue and the practice of abortion. It is possible to obtain small quantities of fetal tissue from spontaneous miscarriages. A more abundant source is tissue taken following elective terminations of pregnancy. In the United Kingdom, this matter was examined by the Polkinghorne Committee in 1989. This body recommended that written consent be obtained from women for use of the fetus or fetal tissue. The matter was also considered by the NBAC study on stem cell research. NBAC recommended that in order to ensure that inappropriate incentives did not prejudice the woman's decision making process directed donation of the cadaveric fetal tissue for EG cell derivation should be prohibited. The recent Nuffield Council paper on stem cell research notes that specific consent ought to be required for any attempt to produce embryonic cell lines from fetal tissue. The Nuffield report goes on to recommend that any consent obtained to the use of fetal material in the establishment of EG cell lines should also cover the use of such cell lines in therapy.

B.3.7. Embryo Research and Abortion

The contemporary debates about the practice of human embryo research are frequently entangled with the issue of abortion. In the United States, for example, abortion has become such a defining political issue that it dominates debate about all life and death issues in contemporary medical practice. (Annas, 1996). The linkage between these two issues need not, however, become such a dominant force. No pregnancy is involved in embryo research, so no termination of pregnancy forms part of the research process. It can be argued that those who oppose abortion could actually support the practice of embryo research because embryo research can both increase the number of pregnancies and reduce the number of terminations. The practice of preimplantation genetic diagnosis allows clinicians to choose not to transfer embryos affected with genetic diseases to the woman. The alternative approach for at-risk couples is to use prenatal diagnosis and termination of pregnancy. Similarly the practice of embryo research into the fertilisation process may increase the number of wanted pregnancies.

B.3.8. The Precautionary Principle

The precautionary principle is one which is familiar in environmental law and ethics. It involves shifting the burden of proof from those who wish to prevent a particular activity or practice to those who wish to pursue it. In effect the precautionary principle requires governments to protect the public health and the environment from threats of irreversible harm.(Cross, 1996). If applied to the issues of human embryo research or cloning the precautionary principle would require researchers to demonstrate that there was a compelling need for society to benefit from the research.

B.4. Regulation of human embryo research: Canada and USA

The practice of embryo research is not restricted by national borders. However, the nature of the technology involved has restricted most of the research to modern industrialised nations. The issue has been subjected to rigorous analysis in North America. The direction of the policy debate in the United States and Canada may yield some insights for European legislators.

B.4.1. Canada

The issue of human embryo research was addressed in Canada by a Royal Commission on the New Reproductive Technologies. This body issued a report entitled *Proceed with Care* which made 293 recommendations on the subject. Subsequently, in 1996, the Canadian government enacted a comprehensive national policy on the management of reproductive technology. The policy had three components: a moratorium, a statute and a regulatory regime. The moratorium was put in place to prevent abuses of reproductive technology in the early stages of the process. The legislation; the Human Reproductive and Genetic Technology Act, explicitly prohibited thirteen practices. These were:

(i) sex selection for non-medical purposes
(ii) buying and selling of egg, sperm and embryo
(iii) germ line gene therapy
(iv) ectogenesis
(v) cloning
(vi) creation of animal-human hybrids
(vii) retrieval of sperm or eggs from cadavers or fetuses
(viii) surrogacy arrangements
(ix) embryo transfer
(x) use of gametes or embryos without the consent of the donors
(xi) embryo research after 14 days of development
(xii) creation of embryos solely for research purposes
(xiii) offering payment for any of the prohibited services

In addition to these specific prohibitions the third stage of the Canadian policy is the establishment of the regulatory regime to monitor those areas of research and practice which are permitted by statute. The policy recommended the creation of an agency which would develop and monitor standards for the use of reproductive materials in medical research. The agency has the power to issue licences to permit these activities and also to inspect premises in order to ensure compliance.

B.4.2. United States

The United States has a long history of controversy in regulating research on human embryos. A distinctly bifurcated approach has developed. Human embryo research which is publicly funded is subject to extremely restrictive regulation. Similar research conducted in the private sector is not, in most states, regulated at all. The debate about

the regulation of embryo research has resurfaced recently due to the developments in embronic stem cell research.

B.4.2.1. Publicly funded embryo research

In 1998 President Clinton asked the National Bioethics Advisory Commission (NBAC) to conduct a review of the issues related to human embryo stem cell research. A year later NBAC produced a report entitled *Ethical Issues in Human Stem Cell Research.* At the centre of this report was the issue of whether federal funding should be made available for human embryonic stem cell research. This is clearly a matter of some relevance to the European Parliament. In 1998 the Parliament attempted to attach an amendment to the Framework V Programme legislation to the effect that resources would not be used to support human embryo research. The European Group on Ethics in Science and New Technologies was asked, as a consequence, by the European Commission to deliver an opinion on the question of human embryo research. In the United States the NBAC report recommended that:

(i) federal funding for embryo research should be restricted to the use of cadaveric fetal tissue and supernumerary embryos, with appropriate safeguards;
(ii) federal funding should not be available for research involving the derivation or use of human embryonic stem cells created solely for research purposes;
(iii) federal funding should not be available for research involving embryos created through SCNT;
(iv) donors of supernumerary embryos should be provided with adequate information to facilitate informed and voluntary choices;
(v) embryos and cadaveric tissue should not be bought and sold;
(vi) a National Stem Cell Oversight and Review Panel should be established to ensure that all federally-funded research is conducted in accordance with ethical principles.

The legality of funding human embryonic stem cell research was the subject of a memorandum issued by General Counsel Harriet Rabb of the Department of Health and Human Services who advised the director of the NIH that the federal ban on funding embryo research did not apply to stem cell research. The reasoning was that, since embryonic stem cells are pluripotent rather than totipotent (i.e. they cannot give rise to a whole organism), they are not to be considered as human embryos within the terms of the statutory definition. Counsel Rabb wrote:

> "Pluripotent stem cells are not organisms and do not have the capacity to develop into an organism that could perform all the life functions of a human being - in this sense they are not even precursors to a human being. They are, rather, human cells that have the potential to evolve into different types of cells."(Robertson, 1999).

Consequently, while federal funding could not lawfully be used for the derivation of embryonic stem cells it could be used for research upon them.

The position in relation to non-federally funded research projects in the United States is signficantly more liberal. The NBAC report recommended that, where embryo research was funded in the private sector, researchers should be encouraged to adopt the recommendations outlined above. Privately funded embryo research projects will, of course, be subject to the terms of relevant state legislation. As the Table below outlines there is relatively little state legislation on the topic.

B.4.2.2. Privately funded embryo research

Only ten states have enacted legislation which explicitly regulates the practice of embryo experimentation by private sector organisations. In the other forty states embryo research conducted in the private sector is subject only to the regulatory mechanisms associated with the Food and Drug Administration (FDA) where applicable.

State Regulation of Embryo Research in the United States.

State	Pre - implantation Genetic Testing	Basic research	Embryo donation	Storage	Gene Therapy	Cell line growth
Florida	✘	✘	✔	✘	✔	✘
Louisiana	✘	✘	✔	✔	✔	✘
Maine	✘	✘	✘	✔	✔	✘
Massachusetts	✔	✘	✘	✘	✔	✘
Michigan	✔	✘	✘	✘	✔	✘
Minnesota	✘	✘	✔	✔	✔	✘
North Dakota	✔	✘	✘	✘	✔	✘
New Hampshire	✔	✔	✔	✔	✔	✘
Pennsylvania	✘	✘	✔	✘	✔	✘
Rhode Island	✔	✘	✘	✘	✔	✘

✔ = activity permitted
✘ = activity prohibited

B.5. Regulation of human embryo research: EU countries

There is, as yet, no supra-national regulation of embryo research within the European Union. A significant divergence of legal and cultural norms exists and is reflected in the pattern of legislation within member states. Germany, for example, carries an extremely restrictive embryo research law in the Embryonenschutzgesetz, which only permits research which will actually benefit the embryo and which is intended to lead to a pregnancy. In Ireland, the Eighth Amendment to the Constitution is interpreted as an absolute prohibition on embryo research. Other states take a more liberal view and permit research on human embryos within clearly defined limits. The United Kingdom, for example, permits research on human embryos until 14 days after conception within the regulatory oversight of the Human Fertilisation and Embryology Authority (HFEA). Some embryo research is also permitted in Finland, Greece, Spain and Sweden in the first 14 days of embryonic development. A third category of states have yet to enact legislation directly on the subject but are currently engaged in a process of deliberation on the issue of human embryo research. In the Netherlands, for example, consultation is ongoing and legislation may be presented later in 2000.

B.5.1. Austria

The area of embryo research is regulated in Austria by the 1992 Act on Procreative Medicine. This legislation severely restricts research on human embryos. The guiding principle of the legislation is that reproductive medicine is permissible only within the boundaries of marriage or stable heterosexual relationships for the purposes of procreation. (Bernat, 1996). The Act states that embryos may only be used for implantation into the woman from whom the oocytes originated. They cannot be used for any other purpose. The number of ova which can be fertilised is also restricted. Only those ova which are likely to be implanted can be fertilised. The donation of embryos or gametes is explicitly forbidden. The Act does permit the storage of embryos for up to one year after which time they must be destroyed.

B.5.2. Denmark

In Denmark Law No. 460 passed on 10th June 1997 regulates artificial fertilisation in connection with medical treatment, diagnosis and research. Article 25 of the law states that research on human embryos can only take place where the purpose is to:

- Improve *in vitro* fertilisation or similar techniques intended to bring about pregnancy; or
- Improve techniques for the genetic testing of a fertilised oocyte with a view to establishing the possible presence of a serious hereditary disease or chromosomal abnormality.

The creation of embryos for any other purpose is prohibited. The law also prohibits any genetic modification of embryos where those embryos are to be implanted *in utero*. All

research projects are subject to the approval of an ethics committee. Embryos cannot be sold or exported although they can be donated with the written consent of the progenitors. Embryos can be cryopreserved for up to one year with the consent of the progenitors. No time limit on the performance of embryo research is mentioned in the legislation.

B.5.3. Finland

The Medical Research Act came into force in Finland in April 1999. The legislation applies to embryo research and defines the embryo as "a living group of cells resulting from fertilisation not implanted in a woman's body." Like a number of transnational and European instruments the law explicitly notes that research should respect the inviolability of human dignity. Chapter 3 of the Act explicitly addresses the questions associated with human embryo research. Such research can only be performed by agencies which have received the appropriate licence from the National Authority for Medico-Legal Affairs (*terveydenhuollon oikeusturvakeskus*). The Act adopts a fourteen day time limit for human embryo research. Section 12 lays down the consent requirements which must be met before such research can take place. Research on embryos requires the written consent of the progenitors. If that consent is subsequently withdrawn the research cannot proceed. Section 13 of the Act states that the creation of embryos solely for the purposes of research is prohibited. Any embryos which have been used in research must not be implanted *in utero* or be kept alive for more than 14 days after fertilisation. The Act states that embryos may be cryopreserved for up to 15 years. An interesting feature of the Finnish legislation is that it appears to envisage the possibility of fetal research. Section 14 states that research on a fetus may not be undertaken without the written consent of the pregnant woman. Section 15 explicitly prohibits any research which has the objective of modifying the germ line, with the caveat that such research may be permissible where it is done for the purpose of curing or preventing a serious hereditary disease.

B.5.4. France

The practice of human embryo research in France is governed by the Loi No. 94-654 of 29th July 1994. This legislation governs the donation and utilisation of elements and products of the human body, medically assisted procreation and prenatal diagnosis. This legislation has been supplemented by the Decree No. 97-613 of 27 May 1997 which amends Division 2 of the French Public Health Code by inserting a new section entitled "Studies conducted on embryos *in vitro.*" The use of IVF procedures is restricted to cases where the aim is to assist in procreation. (Latham, 1998). PGD is prohibited except in cases where a clinician has determined that the progenitors have a high risk of giving birth to a child affected by a serious genetic disease recognised as being untreatable at the time of diagnosis. Both partners must give their written consent to any PGD procedure. Research is permitted on human embryos but it can only be carried out:

> " (i) to offer a direct advantage to the embryo concerned, particularly with a view to increasing the chances of successful implantation; or

(ii) to contribute to the improvement of the techniques of medically assisted procreation through the development of knowledge concerning the physiology and pathology of human reproduction."

The legislation imposes a seven day time limit on the practice of embryo research and also states that the cryopreservation of embryos is limited to five years. The law outlines a number of specific prohibitions in terms of embryo research. These include: cloning; creation of hybrids of chimeras; ectogenesis or parthenogenesis; germ line gene therapy; the creation of embryos purely for research purposes and eugenic experiments which could lead to the selection of human beings.

B.5.5. Germany

In 1992 Germany enacted the *Embryonenschutzgesetz* (Embryo Protection Act) which is one of the most restrictive laws in existence in the area of embryo research. It is a criminal statute which threatens up to five years imprisonment for those found guilty of breaching its provisions. (Deutsch, 1996). Beier and Beckman characterise it as:

"the world's most restrictive law as far as reproductive medicine is concerned." (Beier, 1991).

The law prohibits all forms of "consumptive research" on human embryos. Therefore any research which is not explicitly designed to preserve the embryo and facilitate transfer to the uterus contravenes the terms of the legislation. The law defines an embryo as:

"a human egg cell fertilised and capable of developing from the time of fusion of the nucleii, and further, each totipotent cell removed from an embryo that is assumed to be able to divide and to develop into an individual."

The issue of totipotency is particularly important. In German law the totipotent cell must be afforded the same level of protection as the embryo itself. This has significant implications for research involving human embryonic stem cells. The Act creates a number of criminal offences for engaging in practices involving IVF technology. Thus it is an offence under section 1 to:

- attempt to fertilise an egg cell for any purpose other than bringing about a pregnancy in the woman from whom the oocyte originated;
- attempt to fertilise more oocytes than may be reimplanted within one treatment cycle;
- transfer more than three embryos in the same cycle;
- remove an embryo from a woman before implantation is complete in order to transfer it to another woman or to use it for any purpose not designed for its preservation;
- engage in SCNT for the purposes of cloning

Research on the human embryo is only permitted where the objective of the project is to benefit the embryo. Recent advances in stem cell research have prompted debate within Germany about the effect of the *Embryonenschutzgesetz* on the types of techniques pioneered by Thompson and Gearhart. The Deutsche Forschungs-gemeinschaft, (DFG) the central funding agency for academic research in Germany, recently published an analysis of the potential for human embryonic stem cell research. (DFG, 1999). The

DFG noted that, since the procedure of deriving embryonic stem cells from the blastocyst is performed for purposes other than therapy for the embryo, this would be unlawful under the Act. The removal of embryonic germ cells from cadaveric fetuses does not fall within the terms of the Embryo Protection Act because the law only regulates *in utero* implantation. The removal of EG cells from cadaveric fetuses is, therefore, a legitimate act. The cloning of these cells into totipotent cells would, however, be considered as cloning within the terms of the law and would be unlawful. The DFG paper reflects on the consequences of the law and notes that the restriction to only one of the possible means of deriving embryonic stem cells will impose significant limits on research. The DFG states that:

> "An argument in favour of making possible research on and with embryonic stem cells or research on and with totipotent cells generated by nuclear transfer into enucleated oocytes might be the diagnostic and therapeutic potential of this research and the fact that other countries either offer, or consider to offer, such possibilities."

The DFG paper goes on to observe that it might subsequently be ethically "discomforting" to make use of therapeutic products and techniques developed from embryo research having refused to permit the work to take place within Germany.

B.5.6. Greece

The practice of embryo research is not subject to any explicit statutory regulation in Greece. However, the issue is regulated by the General Council for Health. (Dalla-Vorgia, 1996). The General Council issued a Statement in 1988 which has established practice guidelines in the area of assisted reproduction. Embryo research is permitted in Greece. It can take place for up to fourteen days after fertilisation. Research requires the consent of the progenitors and the approval of the appropriate ethics committee. Embryos can be cryopreserved for up to one year. The General Council for Health Statement recommends that supernumerary embryos should not be destroyed but should be stored. Storage and donation of embryos require the written informed consent of the progenitors prior to the IVF process. The Statement explicitly prohibits the practice of cloning.

B.5.7. Spain

In Spain, embryo research is regulated by the 1988 Law on Techniques of Assisted Reproduction. Section 15 of the Law outlines the conditions in which research on human embryos can take place. The progenitors must give their written informed consent to any research procedure. Any research procedure must take place within 14 days of fertilisation and must either be applied research of a diagnostic character or have a therapeutic purpose. Non-therapeutic or diagnostic research can take place but only where the embryos are non-viable and where it cannot be done on an animal model. Section 16 provides a list of eleven areas where research on embryos may be authorized. Section 20 outlines areas of research which are absolutely prohibited. It states that the creation of human beings by cloning is prohibited. The constitutionality of the Spanish

law was challenged before the Constitutional Court in 1996. The Popular Party challenged the law *inter alia* on the ground that it breached the mandatory constitutional protection of human life contained in Article 15 of the Constitution. The Constitutional Court ruled that the right to life extends to all born persons but does not extend to "nascituri." In the case of "nascituri," or unborn human beings, there is no fundamental right to life as such but there is, rather, a constitutionally-protected interest. The challenge to the law on this ground failed.

B.5.8. Sweden

In Sweden embryo research is governed by two statutes, the Swedish *In Vitro* Fertilisation Act 1988 and the Act Concerning Measures for Research or Treatment involving Fertilised Human Ova 1991. The 1988 Act regulates the practice of assisted reproduction. It also permits some research on human embryos. The research must be performed within 14 days of fertilisation and can only be performed with the consent of the progenitors. Any research which seeks to genetically modify the embryo is prohibited. Once the research process has been completed the embryo must be destroyed. The implantation of a research embryo *in utero* is absolutely prohibited. The 1991 legislation addresses the issue of embryo storage. The period for which an embryo may be cryopreserved has been extended from one year to five years following amendments to the law in 1998.

B.5.9. United Kingdom

The practice of assisted reproduction began in the United Kingdom in 1978 with the birth of Louise Brown, the world's first test-tube baby. As a consequence of this technological lead the United Kingdom has developed a comprehensive jurisprudence relating to human embryos. The matter was first considered by the Committee of Inquiry into Human Fertilisation and embryology chaired by Dame Warnock. (Warnock, 1985). This body reviewed all aspects of assisted reproduction as understood at that time and issued a report in 1985. After a protracted parliamentary process, this report formed the basis of the Human Fertilisation and Embryology Act 1990 (HFEAct).

The 1990 Act is unusual in that it established a form of soft or procedural regulation for the practice of assisted reproduction and embryo research. The Act sets up a statutory body, the Human Fertilisation and Embryology Authority (HFEA), which regulates the activities which are authorised under the act. The core of the legislation lies in section 3 which prohibits the creation or use of a human embryo outside the human body without a licence. Three different types of licence can be issued under the Act; a licence to provide treatment services, to store embryos and gametes or to carry out research on embryos. These activities are all subject to a general prohibition and cannot be lawfully done without a licence. Section 3(3) lists a series of activities which cannot be authorised even with a licence. These are:

- keeping or using an embryo after the appearance of the primitive streak;
- placing an embryo in any animal;

- keeping or using an embryo in any circumstances in which regulations prohibit its keeping or use;
- replacing a nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo.

The primary function of the HFEA is to supervise this licencing process. In addition, it also monitors developments in assisted reproduction and issues consultation documents and Codes of Practice. In 1999 a total of 118 licences were issued by the HFEA to clinics in the United Kingdom. Currently, in order for a research licence to be issued, the HFEA must be satisfied that the use of human embryos is "necessary and desirable" for one of the following purposes:

- to promote advances in the treatment of infertility
- to increase knowledge about the causes of congenital disease
- to increase knowledge about the causes of miscarriages
- to develop more effective techniques for contraception
- to develop methods for detecting the presence of gene or chromosome abnormalities in embryos prior to implantation

All applications for research licences are subjected to peer review. The HFEA states that it must be satisfied that the use of human embryos is essential for the purpose of the research before it will grant a licence. The HFEA began operation in 1991 and by August 1999 had received a total of 124 applications for research licences. 102 of these applications were granted. Research has been completed in 63 of these projects. According to the 1999 Annual Report:

> "the main objective of the majority of the projects currently licensed by the HFEA is to promote advances in the treatment of infertility."

In 1998 the HFEA and the Human Genetics Advisory Committee issued a consultation document on human cloning. A report entitled *Cloning Issues in Reproduction, Science and Medicine* was published which drew a distinction between "reproductive cloning" and the use of SCNT for therapeutic purposes. The report was clearly influenced by the potential for therapeutic advancement in human embryonic stem cell research. Consequently, the report recommended to the Secretary of State for health that two new categories be added to the list of purposes for which research licenses could be issued. These were:

- developing methods of therapy for mitochondrial diseases; and
- developing methods of therapy for diseased or damaged tissues or organs.

These are two central areas of attention in human stem cell research. In response to this recommendation the United Kingdom government established an advisory group under the Chair of the Chief Medical Officer. This body has been tasked with examining the scientific implications of SCNT in embryo research. It is expected to report in May 2000.

Table 4: Regulation of Embryo Research in the European Union

State	Law	Research	Time Limits	Storage	Restrictions
Austria	*Act on Procreative Medicine*	✘	-	1 year.	
Denmark	-	✔ With ethics committee approval.	-	1 year with consent of couple.	Purpose of research must be to improve IVF success rates.
Finland	*Medical Research Act 1999*	✔ Under licence. With woman's consent.	14 days	15 years	Embryos cannot be created for research purposes.
France	*Loi 94-654*	✔ With consent. Must be therapeutic for embryo.	7 days	5 years Annual renewal	Prohibitions: Cloning, creation of chimeras, ectogenesis, germ line gene therapy, creation of embryos purely for research.
Germany	*Embryo Protection Law 1992*	✔ Only permitted if embryo will benefit.	-	✘	Any consumptive research is prohibited. Only research where the embryo is not harmed and where a pregnancy is still possible is permitted.
Greece	-	✔	14 days	✔	There is no legislation in Greece but the General Council for Health Statement 1988 regulates the area.
Spain	Law on Techniques of Assisted Reproduction 1988	✔	14 days	5 years	Must be applied research of a diagnostic kind Must be carried out on non-viable preembryos. Prohibitions on cloning, use of embryos for purposes other than procreation.
Sweden	Law 1988:711 Law 1991:115	✔ With consent	14 days	5 years	Research cannot include genetic modification and the embryo cannot be reimplanted.
United Kingdom	Human Fertilisation and Embryology Act 1990	✔ Subject to research licences issued by HFEA.	14 days	5 years initially. 10 years with consent	Non-therapeutic research must be directed towards advances in: infertility treatment, congenital disease, miscarriage, contraception, detecting genetic abnormalities.

B.6. Transnational Legislation on Embryo Research

B.6.1. European Convention on Human Rights and Biomedicine

The European Convention on Human Rights and Biomedicine was finally agreed by the Committee of Ministers of the Council of Europe in November 1996. (Council of Europe, 1997). The Council of Europe was established in 1949 to promote political, legal and cultural cooperation among member states. It is entirely distinct from the European Union, a fact of some significance in relation to the enforceability of the Council's norms.

B.6.1.1. Origins of the Convention

The Parliamentary Assembly of the Council of Europe began drafting a Bioethics Convention in 1991. The Committee of Ministers issued a directive to the Committee on Bioethics to:

> "study the set of problems posed for law, ethics and human rights by progress in the biomedical sciences .. with a view to harmonising the policies of the member states as far as possible".(de Wachter, 1997).

After a protracted and controversial discussion period the Convention was endorsed by all but three of the 39 participating nations in 1996 (Germany, Belgium and Poland) and was signed by five participating nations in 1997.(Dommel, 1997). The Convention marks a significant attempt to address the diverse dilemmas of bioethics through the use of a human rights framework. The Convention consciously follows the model of the 1950 Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR) at times even borrowing language and phrases from the ECHR. The rationale for the adoption of a new Convention rather than simply amending other Council resolutions and recommendations was set out by Palacios, rapporteur to the General Assembly. First, it was argued that advances in biomedicine were moving at such a pace that the laws in the various member states were not able to keep pace with the developments. Secondly, concerns were emerging that given the rapid pace of development, and the fragmentation of approach among member states, "havens" could emerge for research where scientists could exploit lack of regulation in order to evade the legal restrictions in force in their own countries. Autonomy and self-determination are the core principles underpinning the Convention.

B.6.1.2. The Convention and Human Embryo Research

Article 18 of the Bioethics Convention was one of the most controversial issues discussed during the passage of the instrument and was the focal point for a number of redrafted documents. This controversy is evident in the compromise nature of the final provision which states that:

> "1. Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo.
> 2. The creation of human embryos for research purposes is prohibited."

This provision reflects the inherent difficulty involved in reaching an international consensus on the issue of embryo research. Within the 41 nations the regulation of human embryo research ranges from virtually absolute prohibitions on embryo research to tolerance for the creation of embryos purely for research purposes.

B.6.1.3. The Convention and the Cloning Protocol

In 1998 the Council of Europe approved a Protocol to the recent Convention on Human Rights and Biomedicine. The Protocol *With Regard to the Application of Biology and Medicine on the Prohibition of Cloning Human Beings* expressly prohibits the use of cloning technology on human beings. At the time of writing the Protocol has been signed by 29 states. Notably, five Member States (Austria, Belgium, Germany, Ireland, United Kingdom) have not signed or ratified the Protocol. The Protocol states that:

> "1. Any intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited.
> 2. For the purposes of this article, the term human being "genetically identical" to another human being means a human being sharing with another the same nuclear gene set."

The Explanatory Report which accompanies the Protocol notes that the practice of deliberately cloning human beings represents a threat to human dignity involving the predetermination of the genetic constitution by a third party. It is notable, however, that the Report states that the Protocol is not intended to impact on the use of cloning technology for "non-reproductive purposes". It states that:

> "This Protocol does not take a specific stand on the admissibility of cloning cells and tissue for research purposes resulting in medical applications. However, it can be said that cloning as a biomedical technique is an important tool for the development of medicine…. The provisions in this Protocol shall not be understood as prohibiting cloning techniques in cell biology."

This would appear to permit the use of SCNT techniques in human embryonic stem cell research even in states which had signed the Protocol.

B.6.1.4. The Legal Status of the Convention

The fact that the Convention on Biomedicine is an analogue of the European Convention of Human Rights gives a clear indication of the legal status of the instrument. The enforceability of the ECHR in individual member states is determined, in large part, by whether the state in question subscribes to a monist or dualist theory of legal sovereignty. In a monist state a validly enacted international instrument which is accepted by that state will become part of the national law without the need for any further action. In a dualist state like the United Kingdom, such an instrument will require implementation into

national law before it becomes legally binding at a national level. For a significant number of the 39 member states who have signed up to the Convention the legal norms contained therein are already enforceable at a national level. The remit of the Convention may extend beyond those states which are members of the Council of Europe.

In addition to the States involved in drafting the Convention the process was also joined by thirteen "observers." These included six countries and a number of interational committees. Two Committees of the European Union also had observer status in the drafting of the Convention which raises the possibility that the document could be elevated to the status of a fundamental principle of European Community law through the process of judicial interpretation by the European Court of Justice, as has been the case with the European Convention of Human Rights.

B.6.2. UNESCO Declaration on the Human Genome and Human Rights

The United Nations Educational, Scientific and Cultural Organisation (UNESCO) formally adopted the Universal Declaration on the Human Genome and Human Rights in 1996. (UNESCO, 1998). The International Bioethics Committee of the United Nations had been mandated in 1993, by 185 member states, to consider the possibility of establishing an international legal framework for the protection of the human genome.(Lenoir, 1997). The response is in the form of a declaration rather than a legally binding treaty, because of the apparent political need for flexibility. Lenoir argues that the Declaration has a twofold purpose:

> "It protects the rights and liberties of individuals and also enshrines the role of science and knowledge in helping civilisation to progress. The declaration is also designed to remind the international community of its duty of solidarity towards poorer countries from the benefits of biomedical progress."

This attempt to balance the somewhat divergent claims of social solidarity with the protection of individual human rights permeates the entire Declaration. Article 1 states that:

> "The human genome, inasmuch as it underlines the fundamental unity of all members of the human family and the dignity with which each is endorsed, is a common heritage of humanity"

Like the Council of Europe Convention, the legal status of the UNESCO Declaration can be ascertained by comparison with another long-standing international human rights document, the 1948 Universal Declaration of Human Rights. Lenoir argues that the Human Genome document is analagous to the 1948 instrument which, while not strictly binding, is referred to in many jurisdictions as a source of legal inspiration and which has, in fact, been integrated into the modern constitutions of both Spain and Portugal.

The Declaration does not mention the human embryo explicitly. It contains numerous articles reinforcing the need for respect for human dignity in genetic research. Article 10, for example, states that:

> "No research or its applications concerning the human genome, in particular in the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals, or where applicable, of groups of people."

However, the issue as to whether these protections are meant to apply to the human embryo is not explicitly addressed. Article 11 does, however, refer to the possibilities of human cloning:

> "Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted."

In 1999 the 30th Session of the General Conference of UNESCO issued a series of Guidelines for the Implementation of the Universal Declaration of the Human Genome and Human Rights. The accompanying literature notes that the impact of the Declaration will be reviewed in 2002.

B.6.3. WHO Resolution WHA50.37

At the 50th World Health Assembly the World Health Organisation passed resolution WHA50.37 requesting that the Director-General clarify the potential applications of cloning procedures in human health and their ethical, scientific and social implications. A study group was established to examine the issues. This group presented a report to the 51st World Health Assembly. This report noted that:

> "the main objection to the use of human cloning for reproductive purposes is that it would be contrary to human dignity as it would violate the uniqueness and indeterminateness of the human being."(WHO, 1998).

The focus of the WHO analysis was the issue of reproductive cloning. The major ethical concerns identified were the increased objectification of human beings and intolerance of actual or perceived genetic defects. The report also identified social concerns with the practice of cloning. These included the potential to disrupt intergenerational relations and family structures, the reinforcement of societal prejudices and a consequent increase in discrimination. The report also expressed concern about the threats posed by the commercialisation of cloning technology. The report did consider the possibility of non-reproductive cloning technology, but seemed to suggest that the technical difficulties meant that the process would inevitably clash with most regulatory frameworks by requiring embryonic development beyond the fourteen day period.

Resolution WHA51.10 was passed at the 51st Assembly. The document reaffirmed that cloning for the replication of human individuals was ethically unacceptable and contrary to human dignity and integrity. However, the Assembly went on to request that the Director-General keep the potential of non-reproductive cloning under review. Resolution WHA 51.10 requests that the Director-General:

> "establish a group, involving also government experts, with the aim of clarifying concepts and developing guidelines relating to the use of cloning procedures for non-reproductive purposes."

The issue of human cloning was considered again by the 52nd World Health Assembly in 1999. A working party had drafted a set of draft guiding principles and recommendations

on cloning on medical genetics and biotechnology. The sixth draft guiding principle addresses the process of making policy in the field of biotechnology and states that:

> "Hurried and premature legislation in the rapidly-evolving field of genetics can be counterproductive. Legislation and guidelines should be based on a full and sound scientific assessment of the techniques concerned."

The issue of cloning is explicitly addressed in draft principle 25 which states that:

> "major clinical therapeutic benefits may come from the development of cloning techniques for the production of human tissues and organs from non-embryonic cells. Relevant research should be undertaken provided that it does not involve reproductive cloning and that such applications are developed in conformity with ethical and legal requirements."

It is notable that these recommendations do appear to consider the possibility of non-reproductive cloning for non-therapeutic purposes using human embryonic cells. The matter is addressed in principle 28 which noted that non-reproductive *in vitro* cloning research has important potential benefits. The guidelines state that animal research in this area would be acceptable provided that CIOMS guidelines on the use of animals in research were properly observed. The issue of using human embryonic cells in this research is one which is stated to require the development of further guidelines. The issue of human cloning is to be considered again by the 53rd World Health Assemby in May 2000.

B.7. European Union Legislation

B.7.1. Parliamentary Resolutions

The European Parliament has passed three resolutions which address the diverse issues which arise through the practice of human embryo research.

B.7.1.1. Resolution on Genetic Engineering (1989)

The resolution on genetic engineering was the first of two important biotechnology resolutions passed by the European Parliament in 1989. Although technology has advanced rapidly in the intervening years a number of the provisions of this resolution have an important resonance for current events. The resolution calls for legislation prohibiting any gene transfer to human germ line cells. It also states that the legal status of the human embryo ought to be defined in order to provide unequivocal protection of genetic identity. A substantial proportion of the resolution addresses the issue of embryo research. The resolution states that the zygote needs protection and must not be subjected to arbitrary experimentation. This explicit reference to the zygote would seem to have implications for stem cell research which currently involves work on the preimplantation

embryo or zygote. The resolution does envisage some possible research on embryos but states that such experiments would only be justified:

> "if they are of direct and otherwise unattainable benefit in terms of the welfare of the child concerned and its mother and respect the physical and mental integrity of the woman."

Paragraph 36 of the resolution is also of interest in light of the possibilities of stem cell research. It states that it should be a criminal offence to keep embryos alive with a view to removing tissues or organs as the need arises. Similarly paragraph 41 states that the only possible response to the practice of human cloning is to make it a criminal offence.

B.7.1.2. Resolution on IVF (1989)

The second resolution passed in April 1989 addressed artificial insemination *in vivo* and *in vitro.* This resolution takes a strong line against many of the practices which are central to current modes of embryo research. Paragraph 5 of the resolution calls for the number of embryos to be limited to the number that can actually be implanted. Paragraph 7 calls for a prohibition on any form of genetic experimentation outside the womb. The resolution states that embryos should not be cryopreserved in any circumstances for a period in excess of three years.

B.7.1.3. Resolution on Cloning (1997)

On March 12, 1997, the European Parliament responded to the controversy created by the cloning of an adult sheep at the Roslin Institute in Scotland by passing a resolution calling for a worldwide ban on human cloning. (Heagle, 1998). The Parliament called for all funding for cloning research to be stopped and suggested that penal sanctions should be imposed on any violation of the ban. The resolution states that:

> "in the context of fertility treatment, preimplantation diagnosis, tissue transplantation or for any other purpose whatsoever, cloning cannot under any circumstances be justified or tolerated by any society, because it is a serious violation of human rights."(European Parliament, 1997).

The Parliament noted that every individual was entitled to his or her genetic identity without interference from cloning, but called upon the Commission to consider whether cloning could form part of any EU funded research projects. Notably the Resolution also called for the establishment of a European Union Ethics Committee to monitor developments in the field.

B.7.2. Directives

B.7.2.1. Directive 98/44/EC on Legal Protection of Biotechnological Inventions

The controversy about animal reproductive cloning led the European Parliament to demand that the Commission take action to restrict the possibilities for human cloning. The European Commission responded by drafting the biotechnology directive. This was

developed pursuant to a report by the Group of Advisers on the Ethical Implications of Biotechnology.(GAEIB, 1992). The opinion issued by the GAEIB recommended that, in view of the need to protect human dignity:

> "genes and partial gene sequences whose functions are unknown should be made expressly unpatentable …. In due course, the Community should try to arrange an international agreement on the patentability tests for inventions resulting from genetic research programmes."

The Directive 98/44 governs biotechnological invention by prohibiting the granting of patents for processes involving human cloning. Animal cloning processes may still be the subject of patent applications. The Directive became effective in July 1998 and must be implemented by the Member States by July 20, 2000.

B.7.3. Decisions

B.7.3.1. Decision 182/99 concerning the Fifth Framework Programme

The issue of the ethical implications of resources was considered in decision 182/99 which states in Article 7 that:

> "all research activities conducted pursuant to the fifth framework programme shall be carried out in compliance with fundamental ethical principles, including animal welfare requirements, in conformity with Community law."

The source of the fundamental ethical requirements or the development of any monitoring mechanism is not discussed further in the decision.

B.7.4. Commission Opinions

B.7.4.1. Group of Advisors on Ethical Issues in Biotechnology (1997)

The GAEIB examined the issue of human and animal cloning at the request of the Commission. An opinion was duly issued in May 1997. (GAEIB, 1997). The Group noted that the creation of genetically identifical individuals using cloning technology raised serious ethical questions. They also noted that SCNT research could yield important therapeutic benefits specifically "the development of appropriate stem cell cultures for repairing human organs." The Group went on to recommend that:

> "As far as reproductive cloning is concerned….considerations of instrumentalization and eugenics render any such acts ethically unacceptable. In light of these considerations, any attempt to produce a genetically identical human individual by nuclear substitution from a human adult of child cell ("reproductive cloning") should be prohibited."

The Group did reflect on the implications for human embryo research of restrictions on the use of cloning technology. A caveat was entered which stated that, in those Member States where non-therapeutic human embryo research was permitted, research projects

involving cloning would only be permitted where the objective of the project was to shed light on the cause of human disease or to alleviate suffering. The Group stated that research of such a type should not involve the replacement of the manipulated embryo in the uterus.

B.7.4.2. EGE Opinion on Human Embryo Research (1998)

The GAEIB was replaced in 1998 by the European Group on Ethics in Science and New Technologies (EGE). The remit of the EGE, based on the principles laid down in the European Treaties, is to draw up common rules to enable the internal market to operate in accordance with the ethical values of Europe. The three main objectives of the EGE, indicated at its inauguration, are:

- To help break down barriers between disciplines in fields which require a multi-disciplinary approach, not only scientific and legal, but also philosophical, sociological and economic;
- To provide European decision-makers with clear and up-to-date information, enabling them to be properly informed in carrying out their duties;
- To promote dialogue that stimulates mutual tolerance so that all viewpoints can be expressed before community authorities decide on appropriate regulations.

In 1998 the European Commission requested an EGE opinion on the ethical aspects of research involving the use of human embryo in the context of the 5th Framework Programme. The opinion noted that there was a degree of consensus among those Member States where embryo research was allowed. The rules normally prohibited the implantation of research embryos and the use of embryos for research after fourteen days. The EGE also noted that there was a lack of consensus on the moral status of the human embryo but that views clustered around two positions:

- That human embryos are not considered to be human beings and consequently have a relative need for protection; or
- That human embryos have the same moral status as human beings and consequently are equally worthy of protection.

In the opinion the EGE observes that it would be both legally difficult to seek harmonisation of national laws and inappropriate to attempt to impose one exclusive moral code. The EGE was asked to respond to a proposed amendment which would exclude embryo research from funding under the Framework V research programme. The EGE responded that funding should not "a priori" be excluded but should only be granted under strict conditions. The opinion recommends that protocols seeking funding for embryo research should be subjected to systematic ethical evaluation at Community level.

Part C: Technical File

C.1.0. Glossary of Terms

Adult Stem Cells - stem cells found in the adult organism that replenish tissues where cells have a limited life span.

Autosomal Dominant Disorders - disorders where inheritance of a mutation from one parent only can be sufficient for the person to be affected. Examples include familial hypersholestorolaemia, Huntington's disease and adult polycystic kidney disease.

Autosomal Recessive Disorders - disorders where a mutation must be inherited from both parents for a person to be affected. Parents are usually unaffected carriers. Examples include cystic fibrosis, sickle cell disease and thalassemia.

Blastocyst - a mammalian embryo in the cellular stage of development. It consists of an outer layer of trophoblast surrounding an inner cell mass. The trophoblast will later from the placenta. The inner cell mass will develop into the embryo.

Chromosome - small bodies within the nucleus of every cell in the body. Chromosomes contain the genes.

Cryopreservation - the freezing of oocytes, spermatozoa or embryos and their storage in liquid nitrogen.

Embryo - (i) beginning of an organism in the early stages of development, (ii) in humans, the stage of development between the second and eighth weeks following fertilisation.

Embryonic Stem Cells - cells derived from the inner cell mass of a blastocyst embryo.

Embryonic Germ Cells - cells derived from precursors of germ cells from a fetus.

Gamete - the male sperm or female egg.

In Vitro Fertilisation - the process where the woman's ova are extracted and fertilised *ex vivo* before being returned to the uterus after they have reached the embryonic stage.

Multipotent Cells - cells that can differentiate into a smaller range of cell types and arise later during fetal stages of development.

Pluripotent Cells - cells, which are present in the early stages of embryonic development, that can generate all of the cell types in a fetus and in the adult that are

capable of self renewal. These cells cannot develop into an entire organism (see **Totipotent Cells**)

Preembryo - the mammalian organism in the first fourteen days of development after conception.

Primitive Streak - a transient, opaque line which marks the head-to-tail axis of the embryo. Before the primitive streak appears twinning may occur or two preembryos may fuse into one. The appearance of the streak marks the initial organisation of a single individual.

Reproductive Cloning - reproduction of an entire animal from a single cell by asexual reproduction.

SCNT - somatic cell nuclear transfer is the technique used to clone organisms. It involves inserting the nucleus from a diploid cell or another egg into an egg from which the nucleus has been removed.

Stem Cells - cells which have the ability to divide indefinitely and to give rise to specialised cells as well as to new stem cells with identical potential.

Therapeutic Cloning - medical and scientific applications of cloning technology which do not result in the production of genetically identical fetuses or babies.

Totipotent Cells - cells having the capacity to differentiate into the embryo and associated embryonic membranes and tissues. These cells contribute to every cell type of the adult organism.

X-linked Disorder - disorders due to a mutation on the X-chromosome. X-linked disorders usually affect only males, but can be transmitted through non-affected female carriers.

Zygote - the cell created from the fusion of two gametes in sexual reproduction.

C.2.0. Embryonic Stages

The human embryo and fetus passes through a number of developmental stages. Fertilisation occurs in the fallopian tubes as a result of the fusion of sperm and oocyte. This fusion leads to the production of a zygote. In the period following fertilisation several cell divisions or cleavages occur.

The first cleavage occurs approximately 36 hours after fertilisation when the zygote divides into two cells called blastomeres. At around sixty hours after fertilisation these cells divide again to form four blastomeres. At seventy two hours a further cleavage occurs and an eight cell body is formed. As this process progresses the blastomeres become smaller in size. At the eight cell stage the blastomeres remain unspecialised and have the potential to develop into any cell type of the embryo or into any of the essential tissues and membranes needed to support the development of the embryo. At this stage the blastomeres can be described as totipotent. Removal of one or more of the blastomeres will not affect the capacity of the remaining blastomeres to develop into a fetus.

When the cells divide again into sixteen blastomeres the zygote becomes a morula. Three to four days after fertilisation the morula leaves the fallopian tubes and progresses into the uterine cavity. The morula will remain in the uterine cavity for four to five days before implanting in the uterine wall.

During this preimplantation period cellular division continues. A cavity called a blastocele appears in the centre of the morula. At this stage the structure becomes know as a blastocyst. This is considered to be the first specialisation event and occurs just before implantation when around one hundred cells have developed. The blastocyst is composed of two categories of cells. An outer layer of cells known as the trophoblast surrounds an inner cell mass of about 30 cells. The trophoblast has an important role to play in implantation in the uterine wall. Once implantation has taken place the zygote becomes an embryo and the cells of the trophoblast rapidly differentiate to form the placenta. The inner cells remain undifferentiated. They can, however, no longer develop into all of the cells needed to give rise to an entire organism and are, therefore, categorised as pluripotent rather than totipotent.

In the period following implantation the cells of the inner cell mass divide to form the embryonic disc. The embryonic disc gives rise to three germ layers, the ectoderm, the mesoderm and the endoderm. At the fourteen day stage the embryonic disc is composed of about 2000 cells. Organised develop begins at this stage leading to the emergence of the first differentiated tissues of the body. The two layered embryonic disc develops into a three layered disc and the primitive streak appears.

C.3.0. *In Vitro* Fertilisation

The process of *in vitro* fertilisation (IVF) involves the completion of the fertilisation process in a petri dish rather than *in utero*. It was first successfully performed in the United Kingdom in 1978. IVF involves the administration of ovarian-stimulating hormones to the woman. These hormones induce multiple egg-containing follicles to mature so that a large number of oocytes can be retrieved from a single treatment cycle. Prior to ovulation these oocytes are surgically removed from the woman. The procedure involves making two or three small incisions in the abdomen through which are inserted the laparascope and the hollow needle that will be used to retrieve the eggs. Sperm which has been obtained from a partner or donor are then introduced into petri dishes which contain culture medium and one oocyte. If fertilisation does occur the embryos are allowed to divide for about three days until they reach the two to eight cell stage. They are then implanted immediately, discarded, used for research purposes or cryopreserved for future use. (Perry, 1992).

C.4.0. Reproductive Cloning

Cloning technology has been available in various forms since the 1950s. The current high profile of the practice follows from the controversial cloning of Dolly. The news that the Roslin Institute had successfully cloned a sheep in 1997 led the European Parliament to take an early stance on the subject. A resolution on cloning was passed by the Parliament in March 1997.

Cloning involves the production of a precise genetic copy of a molecule, cell, tissue, plant or animal. It refers to the process of producing individuals who are genetically identical to other living or dead individuals. There are three techniques which may produce a cloned entity. Cloning by embryo splitting involves the division of the preimplantation embryo into equal halves which then produce two genetically identical embryos. This process occurs naturally in humans producing twins. A second technique is cloning by blastomere dispersal which involves mechanically separating the individual cells prior to the formation of the blastocyst. The third technique is that of cloning by nuclear transfer (SCNT). This involves the complete removal of genetic material from a matured oocyte or egg to produce an enucleated cell. This nucleus is then replaced by one containing a full complement of chromosomes from a suitable donor cell which is introduced into the recipient cytoplast. This process was used in the creation of Dolly the cloned sheep. A similar approach has been suggested as a means of avoiding some of the ethical dilemmas associated with embryonic stem cell research. There are major practical and ethical concerns related to such a practice.

C.5.0. Cryopreservation

Cryopreservation describes the process used for freezing embryos. This is generally performed upon supernumerary embryos which are not implanted during a treatment cycle. These excess embryos are frozen in liquid nitrogen at -196 degrees Centigrade.

The purpose of the process is to enable women engaged in infertility treatment to avoid the emotional, physical and financial burdens associated with the oocyte retrieval process. The first pregnancy following cryopreservation was reported in Australia in 1983. (Trounson, 1983). It has been estimated that embryos can be safely stored using this technique for up to fifty years. Worldwide it is estimated that several thousand children have been born from frozen embryos. (Diamond, 1998). In 1997, in the United States over 14 percent of all assisted reproduction treatment cycles involved cryopreserved embryos. (US Department of Health and Human Services, 1999). Pregnancy rates following the use of cryopreserved embryos are, however, significantly lower than in treatment cycles using fresh embryos. In 1997, the United States Centers for Disease Control reported that the live birth rate for cycles using frozen embryos was 18.6 percent, while the rate for fresh embryos was 29.7 percent. (US Department of Health and Human Services, 1999). Beneficial effects which are alleged to arise from cryopreservation include:

- Reduction of the number of ovarian stimulation and retrieval cycles.
- Allows women to preserve procreative capacity after losing their fertility.
- Allows those who are morally opposed to the destruction of embryos to participate in IVF treatment.
- Decreases the incentive to transfer large number of embryos reducing the risk of higher order pregnancies.

However, there are significant ethical and legal concerns related to the disposition of cryopreserved embryos. These concerns tend to arise when the progenitors are no longer willing or able to use the embryos together. In such a scenario there are five possible practical strategies each with concomitant ethical and legal difficulties. (Coleman, 1999). The cryopreserved embryos can be:

- Used by one of the partners to attempt a new pregnancy
- Donated to a third party
- Destroyed
- Donated for use in scientific research
- Cryropreserved indefinitely

Inevitably, given the number of cryogenically preserved embryos, disputes have arisen about their disposition. A number of approaches to resolving such dilemmas have emerged. The first is the contractual approach whereby the dispute is resolved by applying contractual principles to the interpretation of the original decision by the progenitors. Those who advocate this approach suggest that the disposition of the embryo ought to be managed according to the terms of advance agreements drawn up by the progenitors. The second approach is to resolve the dispute in such a way that it favours the partner who seeks to use the embryos. (Silver, 1998). A third is simply to destroy the embryos whenever the progenitors cannot agree on disposition. (Coleman, 1999). A fourth strategy is that developed by the New York State Task Force on Life and the Law which introduced an inalienable rights approach to disposition conflicts. The centrepiece of this approach is the concept of mutual consent. No embryo should be used by either partner, donated to another patient, used in research, or destroyed without the mutual consent of the progenitors. Any objection by either partner must be honoured. In many states explicit legislative norms have been developed which restrict the scope for

choosing one or more of these options. Countries such as Germany, Austria and the Republic of Ireland do not permit embryo research while many other states place limitations on the time period for cryopreservation.

Part D: Annex One

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