Stem Cell Research: Medical Progress with Responsibility

A REPORT FROM THE CHIEF MEDICAL OFFICER'S EXPERT GROUP REVIEWING THE POTENTIAL OF DEVELOPMENTS IN STEM CELL RESEARCH AND CELL NUCLEAR REPLACEMENT TO BENEFIT HUMAN HEALTH

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Executive Summary

1. This report has been produced by an Expert Group established by the Government and chaired by the Chief Medical Officer. The Group was asked to undertake an assessment of the anticipated benefits of new areas of research using human embryos, the risks and the alternatives and, in the light of that assessment, to advise whether these new areas of research should be permitted.

2. It must be emphasised that the report considers and makes recommendations on aspects of cellular research and development. This is basic research which if permitted would precede, probably by many years, any possible application to treatment.

The Stem Cell

3. Many of the scientific issues central to the Expert Group's deliberations concern stem cells, unspecialised cells which have not yet differentiated into any specific type of tissue. The successful application of stem cell research would depend upon:

   - whether stem cells can be successfully isolated and grown in the laboratory;
   - whether stem cells grown in the laboratory can be influenced to turn into specific cell types;
   - whether stem cells that have formed particular cell types could be used to treat patients whose tissue was diseased or damaged through injury;
   - whether tissue grown in this way would develop normally or whether there might be risks to the patient.

Potential Sources of Stem Cells

4. Scientists consider that stem cells could be derived from a number of sources:

   - from early embryos (blastocysts) created by *in vitro* fertilisation – either those which are not needed for infertility treatment (sometimes called 'spare embryos') or created specifically for research;
   - from early embryos created by inserting the nucleus from an adult cell into an egg with its nucleus removed – cell nuclear replacement (sometimes called 'cloning');
   - from the germ cells or organs of an aborted fetus;
   - from the blood cells of the umbilical cord at the time of birth;
   - from some adult tissues (such as bone marrow);
   - from mature adult tissue cells reprogrammed to behave like stem cells.

5. These different types of stem cell are unlikely all to have the same properties or the same potential to develop into particular tissues. Theoretically, stem cells derived from early embryos have the greatest potential to develop into most types of tissue (they are often referred to as 'pluripotent'). Stem cells taken from fetal tissue or umbilical cord blood appear to be more limited in the type of tissue they can be developed into. Stem cells can be extracted from some adult tissues but their potential to develop into

other kinds of tissue is also likely to be limited. It may in the future become possible to reprogramme adult cells to behave like stem cells but at the moment this remains largely hypothetical and requires greater understanding of the mechanisms of reprogramming.

Treatment Possibilities

6. In the long term there could be considerable potential for the use of tissues derived from stem cells in the treatment of a wide range of disorders by replacing cells that have become damaged or diseased. Examples might include the use of insulin-secreting cells for diabetes; nerve cells in stroke or Parkinson's disease; or liver cells to repair a damaged organ. One means of deriving stem cells which are genetically compatible with the person being treated could be from cells created by the cell nuclear replacement technique. Further advances in understanding of how organs regenerate would increase the range of possible treatments that could be considered.

7. In addition to this potential to develop tissue for use in the repair of failing organs, or for replacement of diseased or damaged tissues, the technique of cell nuclear replacement might be applied to treat some rare but serious inherited disorders. Repairing a woman's eggs (oocytes) by this technique gives rise to the possibility of helping a woman with mitochondrial damage to give birth to a healthy child which inherits her genes together with those of her partner.

The Science in Perspective

8. Most scientists in this field see many technical and scientific hurdles to be overcome before the potential benefits of stem cell techniques could be realised. Consequently, it is very difficult to put a timescale on the developments in stem cell research outlined in this document.

9. However, research has shown that stem cells can be derived from embryos in a range of animal species (and, more recently, from human embryos), from fetal tissue, and from adult tissue including bone marrow, skin and blood. Studies, mainly in mice, have demonstrated that stem cells can then be made to differentiate into specific cell types and that cells derived in this way can be successfully transplanted. Applying this work to humans will take considerable time since it would be necessary to identify the chemicals required to encourage the growth of the cells and the appropriate conditions to obtain the required cell type. The research to date does, however, demonstrate why stem cells are regarded as having such considerable potential.

10. Embryos have been created by the technique of cell nuclear replacement in a range of animal species although it is not possible to predict how easy it would be to replicate the work in humans.

11. There are a number of technical and safety issues that have been raised by the early work on stem cells and cell nuclear replacement. These include whether the supply of spare eggs (oocytes) for therapy would be adequate; whether cells and tissues derived from cell nuclear replacement would develop normally or whether defects are likely to arise; whether stem cells and subsequent tissues will "age" normally; whether such tissues will be more prone to develop malignancy; and whether tissues generated from a reprogrammed adult nucleus would overcome the problems of rejection after transplantation as theory suggests they should. All these safety issues would need to be clarified by research. Many would require further study in animals before studies using human embryonic tissue were considered. However, the differences between species mean that human research would be needed both to demonstrate the validity of the concept and to investigate the safety issues.

12. Most scientists consulted felt that the science was still several years away from being able to deliver many of the technical building blocks needed to make significant progress in achieving healthcare benefits. In particular gaining knowledge about how stem cells differentiate, and on how this process might be controlled to produce the particular kinds of tissue needed for treatment, is only just beginning.

Legal Restrictions

13. The UK has a well-established system for regulating the creation and use of embryos, both in research and treatment, embodied in the Human Fertilisation and Embryology Act 1990 (the 1990 Act). This Act is administered by the Human Fertilisation and Embryology Authority (the HFEA). The 1990 Act allows for the creation and use of embryos for research, provided that the research is for one of the five purposes currently specified in the Act and is granted a licence by the HFEA. Before a research project can receive a licence, the HFEA must be satisfied, on a case by case basis, that the use of embryos is necessary for the purposes of the research. Research can only be pursued under the aegis of the Act and with a licence from the HFEA. Embryos used in research cannot be kept for longer than 14 days (excluding periods of storage). Some 48,000 embryos which were no longer needed for *in vitro* fertilisation treatment were used in research between August 1991 and March 1998 and 118 embryos were created in the course of research in the same period.

14. Research involving the creation of an embryo by cell nuclear replacement is not prohibited under the 1990 Act provided it is for one of the existing specified research purposes. In such circumstances, the HFEA would consider each application for a research licence on its merits and would need to be satisfied that the creation of an embryo by cell nuclear replacement was necessary for the purposes of the research. So far no applications for a licence for such research have been made.

15. At present the creation or use of embryos for research to improve understanding or treatment of non-congenital diseases is not permitted under the 1990 Act although there is scope within the Act for additional research purposes to be added through Regulations (rather than new primary legislation).

16. There is no specific legislation currently in force in the UK to regulate research on stem cells once extracted from embryos or research aimed at deriving stem cells from other, non-embryonic, sources such as an aborted fetus or adult cells. A Code of Practice laid down by the Polkinghorne Committee in 1989 governs the use of fetal tissue, while guidance from professional and research bodies and from the Department of Health governs research more generally.

Ethical Considerations

17. A significant body of opinion holds that, as a moral principle, the use of any embryo for research purposes is unethical and unacceptable on the grounds that an embryo should be accorded full human status from the moment of its creation. At the other end of the spectrum, some argue that the embryo requires and deserves no particular moral attention whatsoever. Others accept the special status of an embryo as a potential human being, yet argue that the respect due to the embryo increases as it develops and that this respect, in the early stages in particular, may properly be weighed against the potential benefits arising from the proposed research. The current restrictions and controls on embryo research reflect this latter view, providing the human embryo with a degree of protection in law but allowing the benefits of the proposed research to be weighed against the respect due to the embryo.

18. The derivation of stem cells for research from early embryos no longer needed for infertility treatment ('spare embryos') or created by *in vitro* fertilisation specifically for research does not raise any new ethical issues provided that existing ethical safeguards within the 1990 Act are adhered to. If, as Parliament has

judged, it is ethically acceptable to use embryos for the five currently permitted purposes then those in the ethical middle ground would argue that using them to obtain stem cells to study the development of tissue for potential therapeutic purposes, which offers significant potential benefits in health terms, does not seem to raise fundamentally different ethical issues within the current legislative framework.

19. However, research involving embryos created by cell nuclear replacement raises new concerns for many people, including those opposed to all embryo research and possibly some of those in the middle ground. Even those who accept the current research uses of embryos might express concern about the research use of embryos created in this way. Such embryos can be seen as being created simply as a means to an end and for use as a product source.

20. An alternative view is that the benefits of being able to develop an individual's own cells to create a new source of cells for their own future treatment make this action ethically justifiable. While research on embryos created by cell nuclear replacement does indeed involve using them as a means to an end, this can be said to apply to some degree to all research using embryos. The potential benefits of the research need to be weighed against these concerns. Research into cell nuclear replacement might well offer a means of producing compatible tissue for treatments and it may offer the only means of learning about the mechanisms for reprogramming adult cells. These benefits, if realised, would be substantial and may represent the best prospect of developing treatments for a number of degenerative disorders.

21. Concerns have also been expressed that allowing research on embryos created by cell nuclear replacement would be a first step on a 'slippery slope' towards human reproductive cloning. The Expert Group concluded that an inadvertent slide into reproductive cloning was not a realistic prospect because of the stringent controls operated in the UK by the Human Fertilisation and Embryology Authority in its licensing both of research involving embryos outside the human body and of infertility treatment. The 14 day limit on keeping embryos outside the human body and the very clear position adopted by the Authority that they will not license the implantation of embryos created by cell nuclear replacement, provide clear and effective controls to prevent any access to reproductive cloning. Additional controls would require a new Act of Parliament.

Oocyte Nucleus Transfer

22. Mitochondria are small energy-producing structures in the cytoplasm of every cell, which are only inherited from the mother. The DNA contained in the mitochondria affects a number of important functions in providing energy for the cell. Although the nucleus contains the vast majority of the DNA, defects in mitochondrial DNA are known to cause more than fifty inherited metabolic diseases. In theory it may be possible to prevent a child inheriting damaged mitochondria from the mother by inserting the nucleus of the mother's egg into a donor egg with healthy mitochondria which has had its nucleus removed (a form of cell nuclear replacement). The egg formed in this way would then need to be fertilised by the father's sperm using *in vitro* fertilisation techniques. Any child born would inherit its nuclear DNA from the mother and the father plus healthy mitochondrial DNA from the donor egg. Very little research has been undertaken to investigate whether the theoretical promise of this form of cell nuclear replacement for the prevention of mitochondrial disorders is real.

23. Given the genetic make up of any child born as a result of this technique, it would not constitute reproductive cloning. The resulting child would not be genetically identical to anyone else. Nonetheless, concerns have been expressed that oocyte nucleus transfer represents a modification to the human genome which can be passed on to the next generation. Such modifications are subject to a moratorium in many countries, although basic research to modify eggs or sperm would be permitted under both international conventions and UK law. There does not appear to be any ethical objection to initiating this kind of basic research.

Conclusions and Recommendations

24. The picture presented to the Expert Group by the scientific community was of the enormous potential of stem cells as a source of new tissue for therapeutic uses in the repair of damaged tissue and organs for a wide range of currently incurable disorders. Work in animals and early work to extract stem cells from human embryos support this position. At present, stem cells from embryos appear to have the greatest potential to be developed into the widest range of tissues. In the long term the scientific view is that it will be possible to reprogramme adult cells to make them behave like stem cells with the full potential of embryonic stem cells but without the morally more contestable need to create an embryo.

25. The Expert Group concluded that the great potential to relieve suffering and treat disease meant that research was warranted across the whole range of possible sources of stem cells in the first instance, including embryos.

26. The Expert Group recognised that ethical opinion on the use of embryos in research as a source of stem cells is divided. There are those who believe that an embryo is a human being from the moment of its creation. Others consider that an early embryo is simply a collection of cells. The middle ground, on which the current research uses are based, recognises the special status of an embryo as a potential human being but accepts that it is justified to use early embryos for serious research purposes which may benefit others.

27. While respecting the views of those opposed to such research, the Expert Group concluded that the proposed new research uses to develop treatments for diseased tissues and organs did not raise fundamentally different ethical issues from the research uses currently permitted under the Human Fertilisation and Embryology Act 1990, at least as far as embryos no longer required for infertility treatment were concerned. The potential benefits of the research justified the use of such embryos as a source of stem cells at this early stage of their development.

28. The sensitivity of the issues associated with research involving the creation of embryos by cell nuclear replacement meant that even some people in the middle ground of ethical opinion may not accept that balancing the benefits of the research against the stage of development of the embryo is an appropriate basis for deciding whether to allow this form of research. Nevertheless, the science suggested that such research was desirable. Provided that the necessity of using embryos created by cell nuclear replacement is clearly demonstrated, on a case by case basis, with proper consent of the donors and under the regulatory control of the Human Fertilisation and Embryology Authority, the Expert Group was willing to support it. The Expert Group concluded that the potential benefit of discovering the mechanism for reprogramming adult cells and thereby providing compatible tissue for treatment justifies this transitional research involving the creation of embryos by cell nuclear replacement.

29. The Expert Group recognised that the Human Fertilisation and Embryology Act 1990 does not allow for distinctions to be made in Regulations between the research use of embryos created in different ways, although the manner of regulating any proposed research within the UK is sufficiently finely tuned to be able to take account of particular ethical concerns. Indeed, the UK enjoys a leading international position in the resolution of these difficult questions in that such research is mediated by the Human Fertilisation and Embryology Authority, a statutory body accountable to Parliament with the direct responsibility for reviewing and, if appropriate, licensing research proposals on a case by case basis.

30. The Expert Group considered that this well-established framework for the control of embryo research in the UK provides the necessary safeguards against the inappropriate use of embryos in research. In particular, the Human Fertilisation and Embryology Authority, in considering an application for a research licence for a project involving the creation or use of an embryo by cell nuclear replacement would need to be satisfied that the use of such an embryo was necessary for the purposes of the research

(i.e. that the aims of the project could not be met in other ways including the use of 'spare embryos' generated in the course of treatment services). In addition, specific consent should be sought from individuals whose eggs or sperm have been used in the creation of embryos donated for research to their embryos being used for research involving the extraction of stem cells.

31. The Expert Group noted that there was currently no mechanism for monitoring subsequent research involving cultures of stem cells once they have been extracted from embryos, whether created in the UK or abroad. The Expert Group concluded that while additional controls on individual research proposals were unnecessary in the UK given the controls which would apply to the extraction of stem cells from embryos, it would be desirable for the research to be monitored and progress assessed by an appropriate body to establish whether the research is delivering the envisaged benefits and to highlight any currently unforeseen concerns which may arise.

32. The potential of the technique of cell nuclear replacement to provide treatment to prevent mitochondrial disorders (by oocyte nucleus transfer) led the Expert Group to conclude that basic research should be allowed to investigate that potential. While treatments developed from such research could be seen technically as constituting a modification of the human genome which would be passed on to the next generation, this modification was likely to be of a modest nature. Considerable research would be necessary to investigate the feasibility and efficacy of the technique and the significance of any germ line effect before its use in treatment could be considered. Such basic research is allowed under international conventions.

Recommendations

33. The Expert Group makes the following recommendations:

Recommendation 1

Research using embryos (whether created by *in vitro* fertilisation or cell nuclear replacement) to increase understanding about human disease and disorders and their cell-based treatments should be permitted, subject to the controls in the Human Fertilisation and Embryology Act 1990.

Recommendation 2

In licensing any research using embryos created by cell nuclear replacement, the Human Fertilisation and Embryology Authority should satisfy itself that there are no other means of meeting the objectives of the research.

Recommendation 3

Individuals whose eggs or sperm are used to create the embryos to be used in research should give specific consent indicating whether the resulting embryos could be used in a research project to derive stem cells.

Recommendation 4

Research to increase understanding of, and develop treatments for, mitochondrial diseases using the cell nuclear replacement technique in human eggs, which are subsequently fertilised by human sperm, should be permitted subject to the controls in the Human Fertilisation and Embryology Act 1990.

Recommendation 5

The progress of research involving stem cells which have been derived from embryonic sources should be monitored by an appropriate body to establish whether the research is delivering the anticipated benefits and to identify any concerns which may arise.

Recommendation 6

The mixing of human adult (somatic) cells with the live eggs of any animal species should not be permitted.

Recommendation 7

The transfer of an embryo created by cell nuclear replacement into the uterus of a woman (so called 'reproductive cloning') should remain a criminal offence.

Recommendation 8

The need for legislation to permit the use of embryo-derived cells in treatments developed from this new research should be kept under review.

Recommendation 9

The Research Councils should be encouraged to establish a programme for stem cell research and to consider the feasibility of establishing collections of stem cells for research use.

Chapter 1: Introduction

This Chapter sets out the background to and purpose of the Chief Medical Officer's Expert Group, describes some international responses to the use of cloning techniques and explains the terminology used in the report.

1.1. In June 1999 the Government announced the setting up of an Expert Group chaired by the Chief Medical Officer, Professor Liam Donaldson, to advise on whether new areas of research using embryos should be permitted that could lead to broader understanding of, and eventually to new treatments for, a range of disorders where there is disease or damage to tissues or organs. The decision to set up an Expert Group was a response to the publication in December 1998 of the Human Genetics Advisory Commission and Human Fertilisation and Embryology Authority joint report on *'Cloning issues in reproduction, science and medicine'*.

1.2. That Report drew attention, amongst other things, to the possibility that research using the technique of cell nuclear replacement (in which the nucleus of an adult cell is fused with an egg which has had its nucleus removed) could lead to new treatments for serious disorders by providing a source of new tissue. The Report went on to recommend that the purposes for which embryos can be used in research, which are specified in legislation, should be extended, first to allow for the development of these new treatments for diseased or damaged tissues or organs and secondly to allow the development of treatments for mitochondrial disease.

Purpose of the Expert Group

1.3. The Expert Group was established to assess:

- developments in, and the potential benefits of, stem cell research and research involving cell nuclear replacement;
- the likely timescales of the research;
- possible alternatives to research involving embryos which might achieve the same end;
- the technical and safety issues which might arise from such research.

In the light of this assessment, the Expert Group was asked to advise whether the purposes for which embryos can currently be used in research should be extended. The terms of reference and membership of the Expert Group are at Annex A.

1.4. The Expert Group was not asked to review from first principles the ethical issues of research involving embryos. There is already a strong system of regulation of embryo research in place in this country operated by the Human Fertilisation and Embryology Authority under the Human Fertilisation and Embryology Act 1990. The Expert Group was therefore asked only to consider any new ethical issues that might arise from the creation and use of embryos for the extraction of stem cells for research into new therapies.

1.5. Recognising the range of views on the potential benefits and acceptability of this research, available evidence was evaluated and views were sought on a number of questions (set out at Annex B). Over one hundred responses to these questions were received from researchers working in this field world-wide and from a range of scientific, medical and other bodies and individuals.

The Use of Stem Cells

1.6. The potential to derive stem cells from umbilical cord blood, bone marrow and fetal tissue and for these cells to regenerate themselves has been known for some time. However, the ability to extract stem cells from human embryos and grow them in culture is a more recent advance, opening up a far wider range of treatment possibilities. Two scientific reports published in late 1998 described the first successful isolation and culture in the laboratory of stem cells from human embryos and from fetal reproductive tissue. While the term 'stem cells' is used to refer to any cell which can renew tissue, embryonic stem cells retain the ability to develop into nearly any cell type of the body. It is this potential of embryonic stem cells which suggests the possibility of new therapies.

1.7. The source of the stem cells however raises important ethical issues for many people. On the one hand, the research community and patients suffering from a wide range of incurable disorders are excited by these discoveries and keen to see progress. On the other, there are strongly held views opposed to the use of embryos in this, or indeed any, research.

The Use of Cloning Techniques

1.8. Since the announcement of the birth of Dolly the sheep in 1997, there has been widespread public concern that the new cloning technique of cell nuclear replacement would be used in human reproduction. The UK Government has made it clear that it regards the production of babies through cloning as ethically unacceptable and that it considers this cannot happen in this country as it is regulated under existing UK law. International instruments such as those developed by UNESCO and the Council of Europe have taken a similarly strong stance.

1.9. Many scientists have suggested, however, that the technique which led to the birth of Dolly offers the possibility of providing a source of stem cells which could be genetically compatible with the person being treated. This would be so, it is argued, if the nucleus from a cell taken from the tissue of that person was used in the technique. This could lead to new treatments for diseased or damaged tissue or organs by providing tissue for transplant which would not be rejected.

International Position

1.10. Research of the kind described in this report takes place in a number of research institutes around the world and the issues involved have been considered by a number of international bodies. Most attention has been on human reproductive cloning. UNESCO's *Declaration on the Human Genome and Human Rights* as well as the *Additional Protocol on the Prohibition of Cloning Human Beings* developed under the Council of Europe Convention on Human Rights and Biomedicine concluded that the reproductive cloning of human beings should not be permitted.

Box 1

International Declarations on Cloning

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

UNESCO's Declaration on the Human Genome and Human Rights. Article 11.

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

Council of Europe Convention on Human Rights and Biomedicine: Additional Protocol on the Prohibition of Cloning Human Beings. Article 1.

1.11. Neither UNESCO's Declaration nor the Council of Europe Protocol forbids research in humans involving cloning techniques. In its explanatory note, the Council of Europe indicates that the Protocol does not take a specific stand on whether cloning cells and tissue for research purposes resulting in medical applications should be allowed. It goes on to make it clear that cloning as a biomedical technique is an important tool for the development of medicine, especially for the development of new therapies.

1.12. In the United States of America (USA), the National Bioethics Advisory Commission's report *'Cloning Human Beings'* issued in 1997 concluded that attempting to create a child through cell nuclear replacement (cloning) should be prohibited but that no further regulation was required of the cloning of human DNA sequences and cell lines, fields of research which have already provided important scientific and biomedical advances.

1.13. In response to developments in human embryonic stem cell research, the United States National Bioethics Advisory Commission went on in 1999 to look at and report on *'Ethical Issues in Human Stem Cells in Research'*. The Commission concluded that federal funds should not be provided for the purposes of making embryos solely for the generation of human embryonic stem cells. It considered that research should proceed on stem cells derived from aborted fetuses and embryos remaining after infertility treatment. The extent to which additional sources of embryonic stem cells were required, including from embryos created by cell nuclear replacement, could then be determined. In addition it recommended the establishment of a National Embryonic Stem Cell Oversight and Review Panel to review research proposals involving human (embryonic) stem cells. The United States National Institutes of Health – the body which supports health related research throughout the USA – has subsequently published draft guidelines for stem cell research which would allow for federal funding only for studies using stem cells derived from early human embryos no longer needed for infertility treatment. It would not allow federal funding for research aimed at deriving stem cells from early human embryos, nor for research involving embryos created specifically for research whether by cell nuclear replacement or the fertilisation of an egg with sperm in the laboratory. There is, however, no prohibition of private sector research in this field in the USA, only the use of "federal funds".

Box 2

US National Bioethics Advisory Commission – Recommendations:

- attempting to create a child through cell nuclear replacement should be prohibited;
- no federal funds to be provided for making embryos as a source of stem cells;
- stem cell research to proceed on aborted fetuses and embryos remaining after infertility treatment;
- National Embryonic Stem Cell Oversight and Review Panel to review research proposals involving human embryonic stem cells.

US National Institutes of Health – Draft Guidelines:

- federal funding only for stem cell studies using stem cells derived from embryos no longer required for infertility treatment and from fetuses;
- no federal funding for research to create embryos for research either by cell nuclear replacement or by *in vitro* fertilisation;
- no federal funding for research to derive stem cells from human embryos;
- Human Pluripotent Stem Cell Review Group to be established.

1.14. In Japan, in response to recommendations made by the Bioethical Committee of the Council for Science and Technology (Japan's main science policy body), the Science and Technology Agency produced a draft Bill in March 2000 entitled the *'Law surrounding Human Cloning Technology'*. This Bill would prohibit implanting human embryos created by cloning techniques into the womb of a woman or animal but would allow research using such embryos, subject to strict requirements to be laid down in guidelines. Examples of possible requirements are that there is no alternative to using embryos created by cloning techniques; that it is predicted that the research will be socially useful and progress cannot be made without the use of human embryos; and that sufficient animal experiments have been conducted. Researchers will be required to notify the Government before conducting research and will be subject to penalties (yet to be determined) if they do not conduct their research in accordance with the guidelines.

Terminology Used in the Report

1.15. The Report from the Human Genetics Advisory Commission and Human Fertilisation and Embryology Authority adopted the term "therapeutic use of cell nucleus replacement (CNR)". This was to describe research applications that use cell nuclear replacement and related techniques but which are not aimed at producing identical individuals ('reproductive cloning'). The term 'therapeutic cloning' which has been widely used as a shorthand to describe these research uses has led to much confusion. This report avoids this term and describes the three main technical procedures under discussion. These are:

- studies on the differentiation of stem cells;
- cell nuclear replacement techniques to create embryos up to a maximum of 14 days old for research e.g. to understand nucleus reprogramming;
- oocyte nucleus transfer (in particular for studies using cell nuclear replacement to investigate potential treatments for mitochondrial DNA disorders).

Structure of the Report

1.16. This report seeks to explain the basic science and looks at the potential human health benefits from stem cell and related research and the technical and safety issues that arise (Chapter 2). It then considers the legal and ethical aspects of such research (in Chapters 3 and 4 respectively). Chapter 5 sets out the Expert Group's conclusions and recommendations on research on stem cells and the development of embryos for research by cell nuclear replacement and related matters.

Chapter 2: Cells for Research and Treatment – The Possibilities

This Chapter provides a simple overview of the complex techniques which could yield cells capable of repairing diseased or damaged organs and considers the potential technical and safety issues that arise. Some of the techniques have already been demonstrated in animal research either wholly or partly. Others remain only theoretical possibilities. At their heart lies the concept of a stem cell – an unspecialised cell with the potential to develop into a wide range of mature body tissues. This chapter also examines possible treatment for certain inherited mitochondrial disorders.

2.1. The 20th Century saw a marked and substantial improvement in the health of the population of Britain with expectation of life at birth increasing from 45 years in 1900 to 75 years in 1999. With the fall in mortality and increased longevity came an upsurge in the occurrence of chronic diseases such as heart disease, stroke, cancer, diabetes, Alzheimer's disease and arthritis. This shift meant that by the end of the 1990s many Britons spent years of their lives carrying the burden of chronic diseases rather than enjoying healthy years of life. For example, in 1999, men spent an average of 15 years in ill health whilst women spent an average of 17.4 years in this way. In addition, particularly amongst the young and the elderly, accidents continue to produce injuries that have both acute and long term effects on health.

The Growth of Transplantation

2.2. Diseased or damaged tissues in the adult human body show some natural capacity to repair themselves. However, some tissues do not, whilst others cannot if the disease or injury is extensive. Most organs do not re-grow.

2.3. Challenged by these biological constraints during the second half of the 20th Century, transplantation of tissues and organs within animal species was developed. Blood transfusions were pioneered at the time of the Second World War. The first successful human to human transplant of a major organ took place in 1954 when a kidney was transplanted between identical twins. The recipient survived for eight years before dying of a heart attack. However, kidney transplantation did not become an option for therapy for end-stage renal disease until the early 1960s when drugs to prevent rejection became available. The first heart transplant was carried out in 1968, but the initial results were poor. The UK heart transplant programme began in 1979 and was soon followed by combined heart and lung transplants. Liver transplants also began in the UK in the 1970s, while the Cornea Transplant Service was launched in the early 1980s.

Table 1

Numbers of transplants in the UK and Republic of Ireland in 1998

Heart	281
Heart & Lung	52
Lung	84
Kidney	1767
Liver	694
Cornea	2309

Source: United Kingdom Transplant Support Service Authority

2.4. Four major difficulties have limited the more extensive application of replacement of human tissue by transplantation or grafting.

- Firstly, there are the technical issues. For the established forms of transplantation, the difficulties of surgical technique have largely been overcome. Technical barriers are usually only a problem in the early phase of development of an area of transplantation.
- Secondly, there are problems of tissue rejection. Transplanting tissues from one human being to another or, in animal experiments, from one animal to another (unless they are very highly inbred) leads to the transplanted tissue being identified by the recipient's immune system as 'foreign' and rejected. Over the years, the occurrence of rejection has been reduced by improvements in drugs to suppress the immune response, and, in the case of kidney transplants, by the careful matching of tissue between donor and recipient. However, suppression of the immune system is not without side effects, notably increased susceptibility to infectious disease and a higher incidence of certain types of cancer. The drug regimen to suppress the immune system must be maintained life-long.
- Thirdly, there is the problem of chronic failure of the transplanted organ. This is due both to rejection and to damage occurring to the organ around the time it is retrieved from the donor. So, although 85% of patients who have received kidney and heart grafts still have functioning grafts after a year, by five years only around 65% of grafts survive.
- The fourth and greatest barrier to wider application of transplantation is the availability of tissue and organs. There are over 5000 patients waiting for an organ transplant in the UK currently. Traditionally, organs for transplant have been derived from donations from people who have died, but in the case of kidney transplants there has been an increasing use of generous donations from living individuals. Shortage of organs and tissues for transplantation has led to consideration of other possible options. These have included the use of organs from animals (xenotransplantation) and the use of growth factors to help tissues repair and grow new blood vessels.

The Prospects for Stem Cell Technology

2.5. A new prospect of widely available human tissue that is biologically compatible with the recipient has now been opened up by greater scientific understanding of the growth and development of animal and human cells.

The concept of a stem cell

2.6. At the heart of many of the scientific issues discussed in this report is the stem cell. A stem cell is an unspecialised cell at an early stage of development. Under certain conditions, stem cells can divide and differentiate into a large number of cell types that make up the tissues and organs of the body. In addition they can undergo self-renewal, a process by which an unspecialised stem cell divides to produce two further unspecialised stem cells. The ability of stem cells to self-renew in this way means that a relatively small number of stem cells can be grown in the laboratory into the very large number of stem cells that would be needed for clinical applications. There are different sources of stem cells (Box 3). They differ in the ease with which they can be expanded in number in the laboratory. They also differ in the range and types of mature tissue cells they can be induced to make.

Box 3

Sources of stem cells:

- some adult tissues;
- some fetal tissues;
- umbilical cord blood;
- early embryos;
- reprogrammed adult cells (theoretical).

2.7. The potential of stem cells is that they could be stabilised and grown in the laboratory and then influenced, when required, to differentiate into mature cells or form tissues, such as skin, heart muscle or pancreas cells which produce insulin, which could then be used for treatment. In addition, it is a possibility that cells from mature adult tissue might be reprogrammed to become stem cells: in effect to 'turn the clock back' and make them behave like unspecialised stem cells again.

2.8. The scope for stem cell therapy in the future could be enormous. Organs damaged by trauma or disease do not always need replacing. Repair would be possible if a sustainable source of cells were available. The aim would be to colonise host organs or tissue with sufficient normal cells to restore their physiology or accelerate the repair of damage. The treatment of extensive burns and complex fractures could also benefit from this approach. Some of the potential tissues that could be repaired by these techniques are listed in Box 4.

Box 4

Possible uses of tissue derived from stem cells to treat disease

CELL TYPE	TARGET DISEASE
Neural (nerve) cells	Stroke, Parkinson's disease, Alzheimer's disease, Spinal cord injury, Multiple sclerosis.
Heart muscle cells	Heart attacks, Congestive heart failure
Insulin producing cells	Diabetes
Cartilage cells	Osteoarthritis
Blood cells	Cancer, Immunodeficiencies, Inherited blood diseases, Leukaemia
Liver cells	Hepatitis, Cirrhosis
Skin cells	Burns, Wound healing
Bone cells	Osteoporosis
Retinal (eye) cells	Macular degeneration
Skeletal muscle cells	Muscular dystrophy

2.9. Research has already allowed the first steps to be taken to influence stem cells to produce differentiated cells, but such approaches are a very long way from being able to produce whole, complex organs. It is generally considered that the internal complexity of the structure and function of major human organs such as the kidneys and the heart, with their blood and lymphatic systems and complex tissue structures, make the growth of organs or parts of organs in the laboratory at best a very long term prospect. However, considerable progress could result from the development of cells capable of repairing damage in existing organs.

2.10. The nature of the different sources of stem cells, the current state of knowledge and the technical and safety issues which are predicted to arise are considered in the sections which follow.

Stem cells derived from adult tissue

2.11. Stem cells have been successfully isolated (and cultured) from adult cells of certain tissue types: bone marrow, brain, skin and blood. These have been used for transplantation for some years, for example, in the treatment of leukaemia and in some inherited, single gene disorders. It may be possible to isolate stem cells from certain other adult tissues, but most do not contain stem cells.

2.12. There have, to date, been two major constraints on the use of stem cells derived from adult tissue. First, expanding these stem cells in their unspecialised state in the laboratory has proved problematic. However, this may not remain the case for much longer. The ability to isolate one kind of stem cell from human bone marrow and maintain such stem cells in the laboratory has recently been demonstrated.

2.13. Secondly, the majority of stem cells derived from adult tissue were thought only to have the potential to develop into the type of tissue they were isolated from. However, stem cells from human bone marrow have recently been induced to differentiate into several kinds of cell, including blood, muscle and bone.

2.14. Much of the early work on this approach has been performed in mice, where it appears that more diverse differentiation is feasible. One research group has reported producing a variety of mature blood cell types from adult mouse nerve stem cells. Others have described stem cells from rat bone marrow becoming liver cells and mouse bone marrow stem cells becoming brain cells. This provides some insight into the true potential of stem cell research and contradicts the conventional wisdom that stem cells derived from adult tissue have restricted potential to differentiate. It may be that the long term promise of stem cells derived from adult tissue will equal or even surpass that of embryonic stem cells. However, it is probable that scientific advances from embryonic stem cell research will be necessary to understand how to make greater use of stem cells derived from adult tissue.

Box 5

Stem cells from adult tissue – key features

The technique

- Isolation and growth of stem cells from adult tissues.
- Stem cells found in certain tissue types (e.g. bone marrow and peripheral blood) but not many others.
- Resulting stem cell lines thought until recently only to be capable of differentiating into a limited range of tissue but recent research suggests greater diversity.
- Resulting tissue may be genetically compatible with the person being treated (self-derived) or not (donated).
- Successful transplantation of some stem cells (e.g. from bone marrow) has been possible for some years.

The legal controls (see Chapter 3)

- No specific legal restrictions.
- General legal provisions on removal and use of human tissue apply.

Stem cells derived from fetal tissue or umbilical cord blood

2.15. Two further sources of stem cells are fetal tissue, derived from aborted fetuses, and umbilical cord blood taken at the time of birth.

2.16. It is not yet known what the potential of stem cells derived from fetuses or cord blood is for differentiation into various types of tissue. For example, stem cells from cord blood may only have the capacity to develop into some specific tissues (e.g. bone marrow and blood cells) and not others. In future it may be possible to change the programming of these stem cells so that they mature into types of tissue other than that from which they were derived, but this has not yet been demonstrated.

2.17. Stem cells derived from fetal tissue or umbilical cord blood do not overcome the problems of compatibility and possible rejection for a potential recipient, unless cord blood was to be stored for use by the person later in life. Such a service is now being offered by a number of laboratories in the USA.

Box 6

Stem cells from fetal tissue or cord blood – key features

The technique

- Cells taken from aborted fetuses or umbilical cord blood of newborn babies.
- Tissue sources are readily available and current use is restricted only by the need for consent from the mother.
- Tissues rich in stem cells (e.g. liver) can be extracted and cells successfully grown and concentrated in the laboratory.
- Resulting stem cell lines capable of differentiating but may only be capable of forming some types of tissue and not others.
- Resulting tissue not genetically compatible with the person being treated unless cord blood stored at birth for later use.

The legal controls (see Chapter 3)

- No specific legal restrictions on use of fetal tissue or cord blood.
- Fetal tissue regulated by the (non-statutory) Polkinghorne Code of Practice 1989 which requires approval by a Research Ethics Committee for both research and therapeutic use.

Embryonic stem cells

2.18. Although there is increasing evidence that the types of stem cell described so far may, under some circumstances, be able to change their direction and repair tissues of different kinds, there is one particular type of stem cell which retains the potential to develop into a wide range of cells. This is the embryonic stem cell. Such cells are isolated from very early embryos in the laboratory. Stem cells derived in this way have the potential to develop into a wide range of tissues, such as heart muscle, nerve tissues and bone marrow, and for this reason they are called 'pluripotent'.

2.19. Researchers have already been able to grow stem cells in the laboratory from early embryos of a range of animal species. The majority of research has used mice of particular strains, but other species where success is reported (but not yet replicated) include chicken, mink, hamster, pig, rhesus monkey and common marmoset. One research licence has been issued in the UK by the Human Fertilisation and Embryology Authority for research involving the extraction of human embryonic stem cells.

Stem cells derived from embryos created by *in vitro* fertilisation

2.20. A possible approach to human stem cell research would be to derive stem cells from very early embryos that have been created in the laboratory using donated eggs and sperm or from embryos that have been created during infertility treatment and subsequently donated for research (so-called 'spare embryos'). About five to six days after fertilisation, embryonic stem cells can be taken from the inner cell mass of the blastocyst. The blastocyst begins to form as a 15-20 cell cluster just beginning to separate into identifiable parts that will go on to form the placenta, fetus and other associated tissues. Blastocysts used for the isolation of stem cells would probably have between 150 and 200 cells. After the blastocyst stage the opportunity to extract stem cells is gradually lost as the stem cells start to become specialised and no longer have the potential to become all types of tissue.

2.21. In 1998 a research report from the USA described the successful culture of human stem cells from early embryos (see Box 7). In this work five human stem cells lines were derived from 14 blastocysts (which had been cultured from 36 donated embryos).

Box 7

Stem cells derived from human embryos created by in vitro fertilisation

One group of researchers (in the United States of America) has reported that it is possible to produce a stable cell line in the laboratory derived from human blastocysts. Spare embryos from an infertility clinic were allowed to develop to the blastocyst stage, the inner cell mass isolated and five embryonic stem cell lines were established using techniques already developed using cells from non-human primates. The cell lines were cultured for 4 to 5 months without differentiation but still maintained the potential to form all of the main groups of embryonic germ layers.

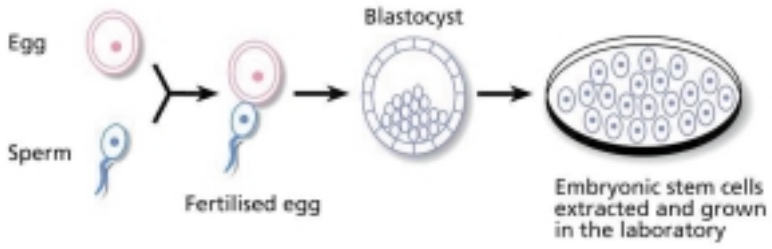
Ref: Thomson J A et al. Embryonic stem cell lines derived from human blastocysts. Science 282, 1145-1147 (1998)

2.22. This work was confirmed in April 2000 when researchers in Australia and Singapore reported that they had isolated human embryonic stem cells from four blastocysts. Cell lines from two of them were successfully maintained in culture for extended periods and the researchers also demonstrated that stem cells can be frozen for storage and grown again once thawed. In further experiments, groups of these stem cells were induced to differentiate into the forerunners of several kinds of body cells. Neural stem cells were then identified and isolated and persuaded to form what appeared to be mature neurons (nerves).

2.23. Such work with human pluripotent stem cells is still at an early stage. Further research will be needed, firstly to establish the best conditions to grow these stem cells consistently without losing their potential to generate new cells and secondly, and much more challengingly, how to persuade them to differentiate in a controlled fashion into particular kinds of tissue.

Figure 1

Embryonic stem cells from in vitro fertilisation – key steps



The ability to encourage embryonic stem cells to differentiate into new tissue

2.24. Research to demonstrate that embryonic stem cells can be made to differentiate into specific kinds of mature tissue cells has so far mainly been carried out in mouse cells. With the proper combinations of growth and differentiation chemicals, mouse stem cells of both embryonic and fetal origin have been made to generate cells which form nerve, blood or heart tissue. Other work in animals has demonstrated that cells derived in this way from stem cell lines can be used for successful transplantation. For example, in both mice and rabbits, stem cells have been extracted, grown in the laboratory, and developed into cardiac muscle cells which, after transplantation into a damaged heart, became incorporated within the heart and beat in time with the cells of the host organ. Mouse nerve stem cells have also been successfully introduced into the brain of rats, producing significant levels of repair in an animal equivalent of multiple sclerosis and, in another study, restoring some movement in the limbs of partially paralysed rats. These findings in particular suggest future possibilities for the treatment of people with brain, spinal cord or peripheral nerve damage.

2.25. Researchers working with animal stem cells have not been able consistently to control the process of differentiation, so much more research would be required to investigate the conditions required to develop specific mature tissue cell types from human embryonic stem cells.

Box 8

Stem cells from embryos created by in vitro fertilisation – key features

The technique

- Embryos are created in vitro from egg and sperm.
- Embryos created in this way can be donated for research when no longer needed for infertility treatment.
- Stem cells are removed after 5-6 days of embryonic cell divisions.
- Resulting stem cell lines could be capable of differentiating into a wide range of tissues.
- Tissue resulting from stem cell culture is not genetically compatible with the person being treated (i.e. rejection has to be counteracted).
- Stem cells have been extracted from embryos in a range of animal species and, in two reported studies, from human embryos.
- In mice, stem cells have been made to differentiate into specific tissue.

The legal controls (see Chapter 3)

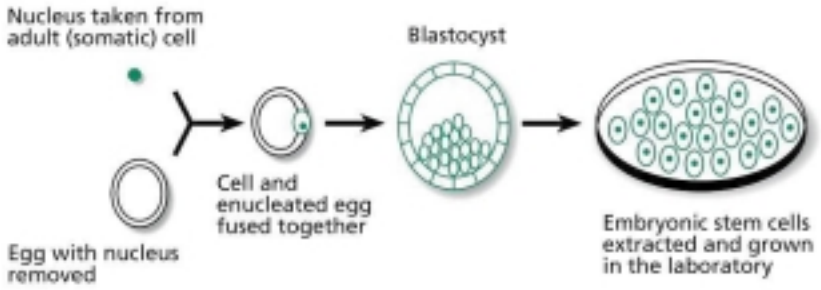
- Creation and use of embryos *in vitro* is controlled by the Human Fertilisation and Embryology Authority (HFEA) under the Human Fertilisation and Embryology Act 1990 (the 1990 Act).
- HFEA has licensed research on human embryonic stem cells but only for the treatment of infertility.
- Use in research to increase knowledge about or develop treatments for non-congenital diseases would require Regulations to be laid in Parliament to extend research purposes allowed under HFE Act 1990.
- Technique would conform to the existing 14-day limit on embryo research.
- Subsequent use of extracted stem cells would be outside the controls of the 1990 Act.

Stem cells derived from embryos created by nuclear replacement

2.26. To date human embryos have only ever been created from eggs and sperm. However, the cell nuclear replacement technique used to create Dolly the sheep shows that embryos can be formed without the use of sperm. Cell nuclear replacement involves inserting the nucleus of a cell from one of the body's organs or tissues into an unfertilised egg (oocyte) which has had its nucleus removed (i.e. has been 'enucleated'). This process is often referred to as cloning. This cell nuclear replacement technique has already been carried out successfully in the laboratory in mammals including sheep, cows, goats, pigs and mice. The resulting cells have been shown to develop through normal embryonic cell division.

Figure 2

Embryonic stem cells from cell nuclear replacement – key steps



2.27. In the case of some animal research this process has been carried through to the birth of an offspring: the experiment with Dolly the sheep is an example. However, if the process is stopped after five to six days (at the blastocyst stage), stem cells can be extracted and grown in the laboratory. It is thought that cells derived in this way would have the same potential as stem cells derived from embryos produced by egg and sperm to differentiate into a wide variety of cell types.

2.28. It is envisaged that tissues developed from stem cells derived from embryos created by cell nuclear replacement would have the advantage of being free from rejection because they should be genetically compatible with the person being treated, from whom the donor nucleus was taken. If this proves to be the case, there is great potential benefit to human health. However, animals born from cell nuclear replacement are not exactly identical to the animal whose cell nucleus was used in the process. They inherit mitochondrial DNA (contained in the outer layer of the egg) from the (enucleated) egg used in the nuclear replacement process. The implications of this for the compatibility of tissue derived from embryos created by cell nuclear replacement are not known.

2.29. Technical questions arise as to whether the cell nuclear replacement technique could ever be successfully carried out using human cells. In addition, possible limitations on the supply of eggs available probably preclude the use of this approach as a treatment option. However it is envisaged that cell nuclear replacement using human eggs will form an important avenue of research if the possibility of reprogramming adult human cells is to become a reality (see paragraphs 2.36-2.38).

Box 9

Stem cells derived from embryos created by cell nuclear replacement – key features

The technique

- Embryos are created by replacement of the nucleus of an unfertilised egg by the nucleus of another cell.
- Stem cells are taken after 5-6 days of embryonic cell divisions.
- Resulting stem cell lines could be capable of differentiating into a wide range of tissues.
- Tissue resulting from stem cells could be genetically compatible with the person being treated (i.e. no rejection).
- Technique of nuclear replacement and establishment of embryonic growth has been successfully accomplished in some animal species.
- Would require supply of oocytes.

The legal controls (see Chapter 3)

- Research involving the creation of embryos by cell nuclear replacement would be permissible for the currently approved research purposes, subject to the controls of the 1990 Act.
- Use in research to increase knowledge about or develop treatments for non-congenital disease would require Regulations to be laid in Parliament to extend research purposes under the 1990 Act.
- Technique would conform to the existing 14-day limit on embryo research.
- Subsequent use of extracted stem cells would be outside the controls of the 1990 Act.
- HFEA has made it clear that it will not license cell nuclear replacement to produce embryos to create a pregnancy.

The feasibility of using the cell nuclear replacement technique in humans

2.30. Producing human embryos by cell nuclear replacement for implantation into the womb would not be allowed as that would lead to reproductive cloning. The rate of success in animals in producing live births, which remains very low in cows, sheep, goats and mice and unsuccessful in rats and rabbits, is not therefore a guide to predicting how easy it would be to create early human embryos by cell nuclear replacement for research. The birth of Dolly the sheep required 277 cell nuclear replacements. However this is not an indication of how many human eggs it would take to produce one blastocyst by cell nuclear replacement. In animals, many blastocysts produced by cell nuclear replacement are lost because they have some defect which makes them incapable of development beyond the stage when stem cell lines could be extracted. Other apparently healthy blastocysts fail to implant in the animal's womb. It has been estimated that 12 or 13 human eggs would be needed to develop one blastocyst by cell nuclear replacement to the stage where embryonic stem cells could be extracted, although this number would be higher if a developmentally 'perfect' blastocyst was required for this process.

2.31. Generalisations from animal experiments are in any event difficult to make. About 1 million mouse eggs were needed to develop mouse *in vitro* fertilisation in the mid 1970s. However, Professors Edwards and Steptoe achieved human *in vitro* fertilisation with just some hundred eggs. Human *in vitro* fertilisation turned out to be easier than might have been expected.

2.32. No applications have been received by the Human Fertilisation and Embryology Authority for a licence for research involving the creation of early embryos by cell nuclear replacement.

Supply of oocytes

2.33. Based upon the early animal research it appears that a reasonable number of human eggs would be needed initially to develop the cell nuclear replacement technique to produce early human embryos. As indicated above, a minimum of 12 or 13 eggs might be required to produce an embryonic stem cell line. The current lack of eggs for fertility treatment suggests a possible shortage of eggs for such research unless there is a breakthrough in the ability to mature eggs in the laboratory. Such a breakthrough is estimated to be some years away. The main source of eggs will therefore continue to be from live human donors. It is doubtful whether this would provide a sufficient supply of eggs to make the cell nuclear replacement technique viable as a basis for treatment in the longer term.

2.34. The alternative of using the eggs of another species, effectively acting as a 'shell' to carry the human cell nucleus, has been suggested. Researchers in the United States of America claim to have used this technique to produce stem cell lines by using an egg from a cow in place of the human egg for cell nuclear replacement and then isolating and growing stem cells from the resulting embryo. This research has not been published. Such a technique would raise many technical and ethical issues. Most researchers active in this field do not regard this as a realistic or desirable way forward.

Stem cells derived from fetal reproductive tissue

2.35. Stem cells very similar to embryonic stem cells have been grown in culture from fetal reproductive tissue. These stem cells are known as embryonic germ cells and have the potential to develop into a wide range of tissue (i.e. they are pluripotent). Such cells have been derived from human fetal tissue obtained after miscarriage or abortion but researchers have not so far been able to culture them for longer than 21 days in the laboratory.

Stem cells derived from reprogrammed adult cells

2.36. Avoiding the use of cell nuclear replacement to create an embryo as a source of stem cells for the treatment of human disease would have considerable advantage, given the concerns surrounding the creation of embryos in that way. One long term goal could be to reprogramme an adult cell to make it revert to its unspecialised state so that it can then be influenced to develop into a different type of tissue.

2.37. Significant increases in scientific understanding of cell development processes, the reprogramming of cells and how the specialised state of cells is maintained are important precursors to achieving this goal. Basic research on stem cells derived from embryos and other sources is one step to developing the necessary understanding. Indeed, not least because of the limited availability of human eggs, many researchers see the very purpose of research involving the creation of embryos by cell nuclear replacement as providing the means of gaining insight into the mechanisms by which an adult cell nucleus can be reprogrammed. Once the way in which an egg with its nucleus removed can reprogramme an adult cell nucleus is understood and controlled, the aim would be to develop stem cells without the need to create an embryo.

2.38. The advantage of being able to reprogramme adult cells would be the ability to develop 'self' tissues of all types to overcome problems of tissue matching and rejection. Sourcing from unrelated tissues could also be used where the tissue to be replaced is diseased or damaged, subject to tissue matching and immune suppression as for current transplantation procedures. In the long term it may also be possible to establish banks of stem cell cultures that have been modified so that they no longer carry the markers that identify them as 'foreign'. This could provide a source of universal donor cells, free from the normal problems of rejection for donated tissues and organs. However this currently remains speculative.

Box 10

Stem cells from reprogrammed adult cells – key features

The technique

- Adult cells would be reprogrammed to behave like stem cells.
- Resulting stem cell lines theoretically capable of differentiating into a wide range of tissues.
- Resulting tissue genetically compatible with the person from whom the cells are taken (i.e. no rejection).
- Research into stem cells and cell nuclear replacement technique in human eggs is probably required as a preliminary stage to develop the knowledge to exploit this technique.
- Technique is not currently feasible.
- Exciting potential but a long term prospect.

The legal controls (see Chapter 3)

- No specific legal restrictions.

Potential Technical and Safety Issues arising in the Production and Use of Stem Cells

2.39. The use of stem cells to provide tissues for therapy raises two major biological problems. One is the risk of tumour formation from incompletely or inappropriately differentiated stem cell transplants and the other is rejection.

2.40. The technique of cell nuclear transfer has opened up the possibility of overcoming the problem of rejection by changing the cell's identity to that of the potential recipient. However, there are potential concerns about the use of stem cells created by cell nuclear replacement. It has been suggested that these may not give rise to as wide a range of normal tissues as stem cells derived from embryos produced in the conventional way. The cells derived may have various functional defects following their reprogramming. Additionally differentiated cells obtained from adult cells may age differently from normal cells. However, evidence for this is currently conflicting. Dolly the sheep has been shown to have cells that appear 'older' than her age but new data from cloned cows suggests that their cells have the characteristics of cells younger than those expected from the age of the animals. A further possible concern is that the prolonged propagation of stem cells in the laboratory might lead to the accumulation of mutations in the transplanted tissue. Mutations could also have arisen in the adult cell used in the cell nuclear replacement process.

2.41. The use of cell nuclear replacement technology to generate human tissues may also carry the risk that, if the cells do not respond normally to differentiation signals before or after transplantation, tumours may arise after grafting. Extensive testing in animal models (such as immune deficient rodents) would be required to assess the likely behaviour of cultured cells transplanted back into the body, their capacity to carry out normal functions and to integrate with existing cells, and their potential to develop tumours.

2.42. The question also arises as to whether the tissue produced from stem cells created by cell nuclear replacement would in fact be exactly matched immunologically to the patient whose cell was used in the process. Embryos created by cell nuclear replacement inherit mitochondria (see paragraph 2.46) from the unrelated egg and it is thought that there is considerable interaction between the nucleus and the surrounding cell during development. The implications of this would need to be investigated.

2.43. Other questions that need to be clarified would include the purity of the tissue derived from stem cells and whether the newly differentiated cells would be 'contaminated' with unspecialised cells; the amount of cells or tissue it would be possible to generate; and the technical challenges of large scale production of cells for therapeutic use.

Box 11

Technical and safety questions

- Would cells and tissues derived from embryos created by cell nuclear replacement develop normally?
- Would they age more rapidly?
- Would there be unpredictable mutations?
- Would tumours arise after transplantation?
- Would the tissue derived be exactly matched immunologically to the patient?
- Would stem cells derived in this way give rise to as wide a range of tissue as stem cells from embryos produced by egg and sperm?
- How 'pure' would tissue derived from stem cells be?
- Is it possible to generate the amount of cells needed for therapeutic use?

2.44. Extensive work would also be necessary in animals to demonstrate the effectiveness of transplanting material derived from stem cells into the tissue needing repair and the long term safety of the technique. Timescales for such work in humans have been estimated as between 3 and 10 years.

Oocyte Nucleus Transfer for Mitochondrial Disease

2.45. A different type of cell nuclear replacement could be used to help women avoid the birth of a child with inherited mitochondrial disease.

2.46. Mitochondria are small energy-producing structures in the cytoplasm of every cell. The cytoplasm can be thought of as a jelly, which holds the nucleus of the cell. Although the vast majority of the DNA is contained in the nucleus of the cell, the mitochondria also contain DNA. We now know that mitochondrial DNA affects a number of important functions related to the role of mitochondria in providing energy for the cell. There is also interaction between DNA in the mitochondria and that in the nucleus.

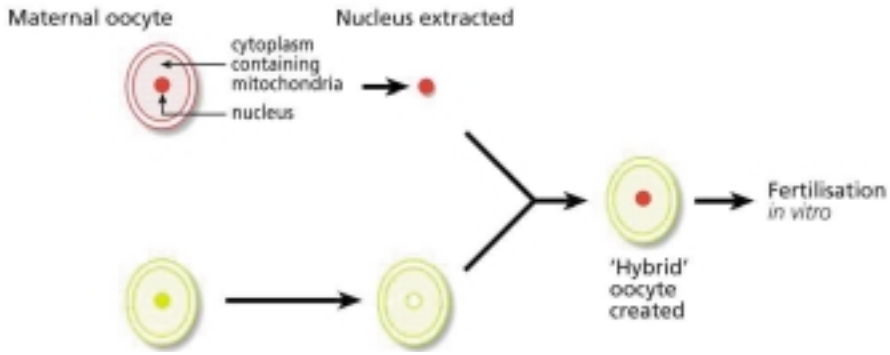
2.47. Tissues with high demands for energy, such as muscle, heart, brain and eye are particularly vulnerable to mitochondrial defects. There are more than 50 inherited diseases of metabolism that are known to be caused by defects in mitochondrial DNA.

2.48. A baby only inherits mitochondrial DNA from its mother because mitochondrial DNA in the sperm does not appear to pass through the process of fertilisation. If the maternal mitochondrial DNA carries a disorder then it will always be passed on to the child.

2.49. If a woman carries the potential to pass on a mitochondrial disease to her child it may become possible to prevent the child from inheriting the disease by the cell nuclear replacement technique. This would involve inserting the nucleus of the mother's egg into a donor egg which has healthy mitochondrial DNA and which has had its nucleus removed. This new egg could then be fertilised by the sperm of the woman's partner by *in vitro* fertilisation techniques. Any child born would have received its nuclear DNA from its mother and her partner but would have healthy mitochondrial DNA from the donor egg. Although this is a form of cell nuclear replacement it is not the same as that described in the previous section as the desired outcome of the process is a healthy egg (requiring fertilisation) and not an embryo.

Figure 3

Treating mitochondrial disease by oocyte (egg) nucleus transfer – key steps



2.50. Very little research work has been carried out to establish whether this theoretical reasoning would be confirmed in experiments and whether the technique would in fact lead to the prevention of disorders of mitochondrial DNA.

2.51. The feasibility and success of the technique would need extensive testing in animal models before being attempted as a research procedure to create early human embryos. The Human Fertilisation and Embryology Authority could be expected to require considerable human embryo research before it considered licensing the approach of oocyte nucleus transfer for treatment.

2.52. At present the only form of clinical intervention that can enable a family with a mitochondrial DNA disorder to avoid having an affected child is *in vitro* fertilisation in which the father's sperm is mixed with an egg donated by another woman. This is not acceptable to many parents because the natural mother is not playing any part in the genetic make up of the resulting child.

2.53. It is not yet possible using oocyte nucleus transfer to produce viable embryos with the capacity to develop to term. Nor are the potential risks to the embryo of defective development understood. It is also not known whether any of the damaged mitochondria would be transferred to the hybrid egg with the healthy nucleus. A study of the genetic make up of ten sheep created by cell nuclear replacement suggests that this should not be the case. These sheep inherited their mitochondrial DNA solely from the (enucleated) egg used in their creation, but this would need to be tested in human eggs.

2.54. The problems over supply of oocytes for research (see paragraph 2.33) would be equally relevant to research into oocyte nucleus transfer for mitochondrial disorders. Research would need to rely on human donors.

Box 12

Oocyte nucleus transfer for mitochondrial diseases – key features

The technique

- The healthy nucleus is taken from the egg of a woman with damaged mitochondria and placed in an unfertilised donor egg (with healthy mitochondria) with its nucleus removed.
- Fertilisation then carried out *in vitro* by combining the newly formed egg with sperm.
- Only way for some mothers carrying a mitochondrial disease to have a genetically related healthy child.
- Technique of nucleus transfer successful in animal species.
- Would require availability of sufficient donor eggs.

The legal controls (see Chapter 3)

- Research into this technique could be licensed by Human Fertilisation and Embryology Authority under current regulations to increase knowledge about the causes of congenital disease or to promote advances in the treatment of infertility.
- Treatment could be licensed by Human Fertilisation and Embryology Authority after adequate research.

Conclusions

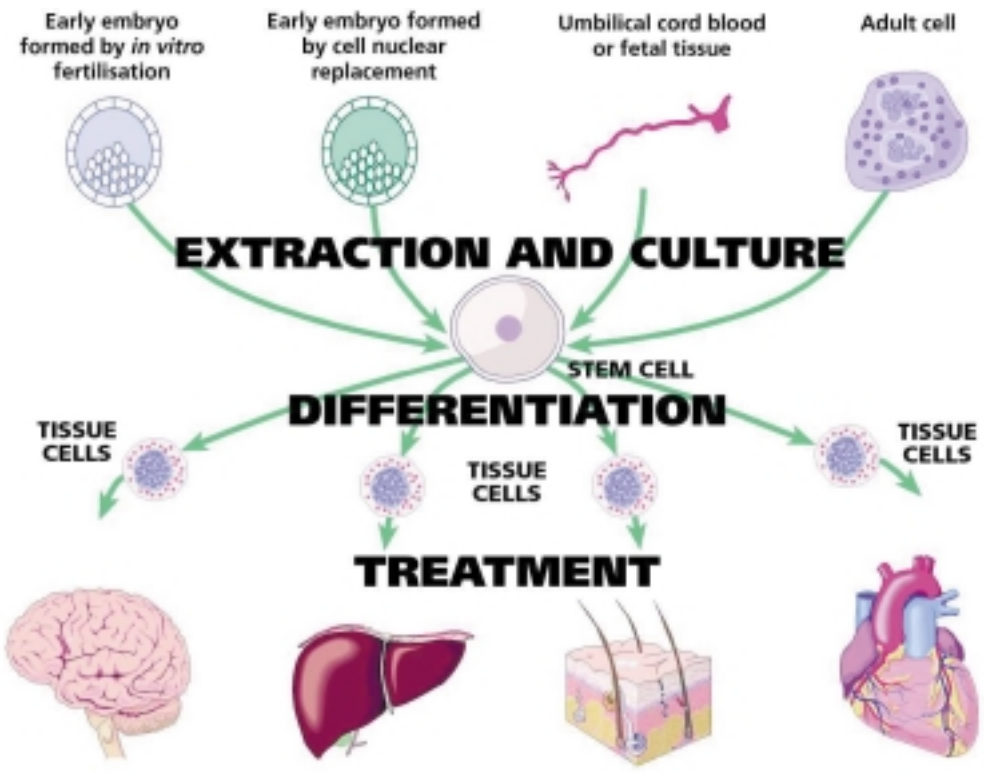
2.55. Research involving the extraction and use of stem cells raises the prospect of a range of exciting new therapeutic possibilities for the repair of diseased or damaged tissues in the future, which could eventually bring major health benefits.

2.56. The potential of stem cells as a source of new tissue for use in this way has been demonstrated, in principle at least, in stem cell research in animals, the majority of which involved mice. The limited use of stem cells derived from particular types of adult tissue for human therapeutic purposes is a further indication of the possibilities. However, the successful isolation and culture of human embryonic stem cells and stem cells from fetal reproductive tissue in 1998 and the recent confirmation of these findings, together with the demonstration that stem cells can differentiate into neural cells, suggest additional therapeutic possibilities. These stem cells appear at present to have the potential to develop into a far greater range of tissues than adult derived stem cells.

2.57. Based on extrapolation from the animal research and the limited research in human cells undertaken so far the Expert Group concluded that repairing nerve cells lost in Parkinson's disease and Alzheimer's disease, replacing insulin-producing cells in diabetes, changing the outcome of spinal cord injury and multiple sclerosis, replacing lost heart muscle cells in cases of congestive heart failure, bone cells in osteoporosis and liver cells in cases of hepatitis or cirrhosis all seemed realistic prospects if the research fulfilled its potential. However, the Expert Group concluded that the prospect of developing whole replacement organs appeared unlikely for the foreseeable future.

Figure 4

Potential sources and treatment possibilities of stem cells



2.58. Most scientists in the field of stem cell research predict that the scientific and technical hurdles that need to be overcome will require many years of basic research. Before it is possible to use stem cells effectively for therapeutic purposes, fundamental problems in the field of cell and developmental biology will need to be solved. These include the need for better understanding of the origin of the various types of differentiated cells and how the process of differentiation is started and maintained. In the early stages the vast majority of work could be expected to involve animal rather than human cells, although the differences between species means that research on human cells would be necessary to demonstrate the applicability to humans.

2.59. In addition to the animal research, it appears that considerable advances in understanding could be made through exploring the derivation and use of stem cells from spare embryos or from fetal or adult tissue. However these would not address the problem of rejection of tissue nor advance understanding of how adult cells might be 'reprogrammed' to produce new tissue. The Expert Group concluded that research into the technique of cell nuclear replacement offered the best prospect of a solution to these problems.

Box 13

Benefits achievable through research involving cell nuclear replacement with human cells:

- understanding how adult cells can be reprogrammed;
- establishing the role of the egg in reprogramming an adult nucleus;
- discovering whether stem cells derived from embryos created by cell nuclear replacement differentiate in the same way and have the same potential as stem cells derived from embryos created from eggs and sperm;
- clarifying whether the stem cells from embryos created by cell nuclear replacement can produce tissue compatible with the donor of the nucleus;
- clarifying whether concepts developed in animal studies apply to humans, in particular the conditions required to achieve cell nuclear replacement in a human egg.

2.60. Research rarely proceeds in a neat sequential manner. Alternative and complementary approaches need to be pursued in parallel to enable the pieces of the jigsaw to be fitted together and advances to be made. The Expert Group therefore concluded that cell nuclear replacement research would need to proceed in parallel with research to extract embryonic stem cells to offer the best prospect of health benefit in the shortest period of time.

2.61. The Expert Group concluded that there were sufficient demonstrations of principle in the research to date to suggest that further research should be undertaken across the range of possible sources of stem cells. This would enable a better assessment to be made of the true potential of the research and the most fruitful avenues to pursue further. In particular it would enable the feasibility to be explored of producing tissue for an individual which would not be rejected, at the same time as exploring the feasibility of establishing tissue banks of stem cell cultures from the different sources of stem cells. It would also enable the technical and safety questions to be addressed. Subject to the legal and ethical considerations discussed in Chapters 3 and 4, the research should ideally include embryonic stem cells, including those extracted from embryos created by cell nuclear replacement.

2.62. The Expert Group concluded that the use of eggs from a non-human species to carry a human cell nucleus was not a realistic or desirable solution to the possible lack of human eggs for research or subsequent treatment.

2.63. The technique of oocyte nucleus transfer to cure mitochondrial DNA disorders would require considerable research before its possible use in treatment could be contemplated. However, subject to the feasibility and safety of the technique being established, the Expert Group concluded that such research appeared to offer the long term prospect of a healthy child for affected families.

Chapter 3: Cells for Research and Treatment – Legal Considerations

This Chapter sets out the legal framework governing the use of embryos in research and the regulation of stem cells derived from non-embryonic sources.

3.1. The United Kingdom has a well-established system to regulate the creation and the use of embryos for both treatment and research purposes under the Human Fertilisation and Embryology Act 1990 (the 1990 Act). The conduct of medical research is also governed by guidance produced by the Department of Health and a wide range of professional bodies and, if carried out in the NHS, requires approval from a research ethics committee. In this Chapter, the way in which the law currently applies to the issues raised by stem cell research and treatment is described.

The Law Governing the Creation and Use of Human Embryos

3.2. The Human Fertilisation and Embryology Act 1990 was passed after extensive consultation on the recommendations of the Report of the Committee of Inquiry into Human Fertilisation and Embryology (the Warnock Report) published in 1984. The Warnock Committee had been set up after the birth of the first 'test-tube' baby to consider the legal and ethical issues raised by developments in the treatment of infertility and related matters in human reproduction. The 1990 Act gave effect to the majority of the Warnock Committee's recommendations.

Research uses of embryos

3.3. The 1990 Act allows research on human embryos subject to the conditions laid down in that Act being met and to a licence being issued by the Human Fertilisation and Embryology Authority (HFEA) for a specific research project.

3.4. The 1990 Act allows research on embryos which have been created in the course of *in vitro* fertilisation treatment but are surplus to clinical need and on embryos created specifically for research.

3.5. The number of embryos created between 1992 and March 1998 (the latest date for which verified figures are available) and categories of use are shown in Table 2.

Table 2

Embryos created by IVF: 1991 – 1998*

763,509 embryos created
351,617 used in infertility treatment
183,786 stored for future treatment
48,444 given for use in research
118 created in the course of research
237,603 not used for any purpose and destroyed.

*Source: HFEA. *1 August 1991 to 31 March 1998*
Embryos may be counted in more than one category

3.6. The 1990 Act currently only permits research using human embryos if such research is necessary or desirable for one of five specified purposes.

Box 14

Research purposes permitted under the Human Fertilisation and Embryology Act 1990*

Research licences can only be issued if the HFEA is satisfied that the research is necessary or desirable for the purpose of:

- promoting advances in infertility treatment;
- increasing knowledge about the causes of congenital disease;
- increasing knowledge about the causes of miscarriages;
- developing more effective techniques of contraception;
- developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.

Additional purposes may be added by "affirmative Regulations" but must be related to increasing or applying knowledge about the creation and development of embryos, or about disease.

**Schedule 2 paragraph 3(2).*

3.7. Even if a research project is for one of the five specified purposes the researchers must apply to the HFEA for a licence. The HFEA must be satisfied that the use of embryos is necessary for the purpose of the specific research proposal before issuing such a licence. Each research licence issued by the HFEA requires the provisions of the 1990 Act to be complied with. In particular, an embryo can only be used in research if the individuals whose gametes (sperm or eggs) have been used to create that embryo have given their consent to its use in research. In addition, the researchers are required to keep such information about the research as the HFEA specifies and the HFEA may impose additional conditions on the licence within the terms of the 1990 Act.

3.8. Under UK law, no embryo grown in the laboratory can be retained for longer than 14 days into its growth cycle. Subject to conditions laid down in the 1990 Act, it is legal to store embryos created *in vitro* for subsequent use in treatment or research. However, when removed from storage they cannot be kept beyond the 14 day limit.

3.9. Research involving the use of embryos to extract stem cells is permitted currently under the 1990 Act provided that the research is for one of the five specified purposes. A licence for one such research project has been granted.

3.10. The HFEA has not to date received any application to conduct research involving the creation of an embryo using cell nuclear replacement. The use of this procedure in research is not banned by the 1990 Act, although the research could only be carried out currently if it was for one of the five specified purposes. In addition the HFEA would need to be satisfied that the creation of an embryo in this way was necessary for the purposes of a specific research project.

3.11. The 1990 Act does not apply to the keeping of, or research on, stem cells once extracted from an embryo and grown in the laboratory.

3.12. At present the creation or use of embryos for research to improve understanding of, or treatment for, non-congenital diseases cannot be authorised under the 1990 Act. That Act does however allow for other research purposes to be added by "affirmative Regulations" (i.e. Regulations which have to be debated in each House of Parliament before they can come into force). The purposes which may be added are restricted by the 1990 Act to research which would increase knowledge about the creation or development of embryos, or about disease, or which would enable such knowledge to be applied.

3.13. The possibility of using the egg of a non-human species to carry a human nucleus had been suggested by one reported research project in the United States of America. The 1990 Act does not allow the mixing of human and animal gametes except under extremely limited circumstances for testing the viability of sperm. However, mixing other human cells with an animal egg is not specifically prohibited under the 1990 Act.

Box 15

Controls on embryo research under the Human Fertilisation and Embryology Act 1990

- Research projects involving creating embryos *in vitro* or keeping or using embryos require a licence from the HFEA.
- Licences are only issued if HFEA is satisfied that the use of embryos is necessary for the purposes of the research.
- Embryos used in research may not be kept after 14 days (excluding storage).
- Embryos can only be used in research if the individuals whose eggs or sperm are used in the creation of the embryos give their consent.

The use of embryos for treatment

3.14. If research into the extraction and differentiation of stem cells from embryos is allowed and is successful, the question could arise in the future of allowing the creation or use of embryos to develop tissue specifically for treatment purposes. This would arise for example if an embryo had to be created by cell nuclear replacement for each patient to provide compatible tissue. At present the only treatment services using embryos which can be licensed under the 1990 Act are medical, surgical or obstetric services to help women to "carry children". The possibility of an amendment to the Act would need to be considered by Parliament if the research suggested that the use of embryo-derived cells for broader treatment purposes was necessary and acceptable.

Human reproductive cloning

3.15. The creation of an embryo through cell nuclear replacement for subsequent implantation into a woman's womb to produce a baby cannot take place in the UK. This is the technique most commonly referred to as cloning. A licence from the HFEA would be required for the creation of human embryos using this method of cloning. The HFEA has made it clear that as a matter of policy it will not issue a licence for treatment involving the use of embryos created in this way.

Regulation of the Derivation of Stem Cells from Non-embryonic Sources

3.16. As Chapter 2 has shown, stem cells may be obtained from a number of sources other than embryos.

3.17. The use of fetal material as a source of stem cells would fall under the terms of the Code of Practice on the Use of Fetuses and Fetal Material in Research and Treatment drawn up by the Polkinghorne Committee in 1989. That Committee addressed the potential ethical concerns about the use of tissue from aborted fetuses and laid down a series of principles which still apply to obtaining and using such tissue (see box 16). All proposals for the use of fetal tissue whether for research or novel therapies must be referred to a research ethics committee for approval.

Box 16

The Use of Fetuses and Fetal Material in Research and Treatment: the Polkinghorne guidelines.

Principles governing the use of fetal tissue

- There should be clear separation between decisions and actions relating to the termination of pregnancy and decisions and actions relating to the use of the fetal material made available.
- The decision to carry out a termination must be reached without consideration of the benefits of subsequent use of the fetal tissue. Deliberately conceiving or terminating a pregnancy to produce suitable material is unethical.
- The management of the pregnancy should not be influenced by the potential use of the fetus in research or therapy. This includes the method and timing of an abortion or the management of a mother whose fetus dies in the womb or who has a spontaneous abortion.
- No inducements, financial or otherwise, should be put to the mother, or those who may influence her decision, to have her pregnancy terminated or to allow fetal tissue to be used.
- The mother should not be informed of the specific use which may be made of the fetal tissue or whether it is to be used at all.
- The written consent of the mother should be obtained before any research involving the fetus or fetal tissue takes place.
- Consent to the termination of pregnancy must be given before consent is sought to the use of fetal tissue.

In addition all proposals for the use of fetuses or fetal tissue must be referred to a research ethics committee whether the work is classed as research or novel therapy – in recognition of the sensitivity surrounding the use of such tissue.

3.18. If stem cells were taken from adult tissue retrieved after death, the Human Tissue Act 1961 would apply. This governs the use of tissue and body parts from deceased persons both for research and therapeutic uses. Tissue may be obtained from living adults either specifically for research purposes or retained from the adult's treatment (for example, after surgery). Where tissue is obtained specifically for research, an explanation of the proposed use must be given or consent to the removal procedure would not be valid. Similarly the use of cord blood requires an explanation and the mother's consent. The conduct of research on human tissue is governed by guidance from the Medical Royal Colleges and the Medical Research Council. Research projects conducted in the NHS which involve the removal and subsequent use of human tissue require approval from a research ethics committee.

Conclusions

3.19. Given the special status of the human embryo, it has been recognised that some protection is required in law for research uses of embryos. The controls within the Human Fertilisation and Embryology Act 1990 operated by the Human Fertilisation and Embryology Authority, provide a well-established system of regulation for the creation and use of embryos in research. This includes specifying the purposes for which embryos may be used in research; scrutinising individual research proposals to ensure that the use of embryos is necessary for the particular research project; ensuring that the individuals whose eggs or sperm have been used to create the embryo have given their consent to its use in research; and a time limit of 14 days (excluding storage) on keeping the embryo in the laboratory.

3.20. This system of regulation applies to research projects to extract stem cells from embryos for permitted research purposes. The 1990 Act would not apply to subsequent research projects using cultured stem cells originally extracted from an embryo.

3.21. The non-statutory regulation of the use of fetal tissue under the Code of Practice produced by the Polkinghorne Committee in 1989 provides an ethical framework for research or novel therapy involving the use of such tissue.

Chapter 4: Cells for Research and Treatment – Ethical Considerations

Previous Chapters have pointed to the potential benefits to human health of developments in stem cell technology, the likely timescales for such developments and the practical and scientific problems raised. The regulatory framework governing research in these areas has been outlined. However, for many people the major concerns about stem cell technology relate to the source of the stem cells and particularly the creation and use of human embryos for this purpose. Those issues are discussed in this Chapter.

4.1. Few people express concern about the use in research of cells or tissue taken from an adult with his or her informed consent or from cord blood taken with the consent of the mother. Ethical issues concerned with the use of fetal tissue were addressed by the Polkinghorne Committee as indicated in Chapter 3. A number of novel therapeutic uses, such as the transplantation of fetal tissue into patients suffering from Parkinson's disease, have already been the subject of ethically approved trials using fetal tissue. The use of fetal tissue as a source of stem cells therefore appears not to raise new ethical issues. However, the status and use of human embryos in research is more controversial.

4.2. A significant minority of people believes that the use of any embryo for research purposes is unethical and unacceptable on the grounds that an embryo is a human being entitled to full human status from the moment of its conception and, in particular, has the right to life. At the other end of the spectrum there are those who consider that an early embryo is simply a collection of cells, entitled to no greater rights than any other collection of human cells. In the middle ground, the special status of an embryo as a potential human being is accepted, but the significance of the respect owed to developing human life is regarded as increasing in proportion to the degree of development of the embryo. At the very early stages of development, according to this view, it is morally justified to use embryos for research purposes in order to benefit others, provided that such research is necessary and justified by the benefit it may produce in the long run.

4.3. These morally contentious issues were considered by the Committee of Inquiry into Human Fertilisation and Embryology (the Warnock Committee) and debated at length by Parliament during the passage of the Human Fertilisation and Embryology Act 1990. Parliament decided to allow embryo research to take place, but subject to the considerable safeguards enshrined in that Act. The purpose of this Chapter is not to revisit that earlier debate. It focuses only on whether research involving the extraction of stem cells from embryos, or the creation of embryos for such research using cell nuclear replacement, raises any new ethical issues, as the terms of reference of the Expert Group required. In particular it considers whether these new possibilities for research cross a new moral boundary, representing an unjustified extension of the uses of embryos already authorised by the 1990 Act.

Ethical Principles underpinning Current Law and Practice

4.4. The arguments for and against the use of human embryos in research as set out above were considered by the Warnock Committee following wide public consultation.

4.5. The Warnock Committee found that these were difficult issues to deal with and its members were unable to reach a unanimous conclusion. The majority however concluded that research on embryos should be allowed, including research on embryos created for that purpose, but subject to conditions.

4.6. The 1990 Act reflects the majority conclusion of the Warnock Committee. The use of embryos in research in the UK is currently based on the principles expressed in their Report.

Box 17

The principles underpinning the use of embryos in research

- The embryo of the human species has a special status but not the same status as a living child or adult.
- The human embryo is entitled to a measure of respect beyond that accorded to an embryo of other species.
- Such respect is not absolute and may be weighed against the benefits arising from proposed research.
- The embryo of the human species should be afforded some protection in law.

Ethical Implications of an Extension of the Research Purposes in the Human Fertilisation and Embryology Act 1990

4.7. Embryo research is allowed in this country, subject to the conditions set out in Chapter 3 (see Boxes 14 and 15). The specified purposes for which research is currently permitted mostly relate to those intended to lead to improvements in infertility treatment and those which, with the possible exception of research into contraceptive techniques, could be said to be of benefit to future embryos. The use of embryos in these forms of research appears to be accepted in the UK as justifiable. The question then arises as to whether only research related to the development of the embryo and reproduction is morally justified or whether broader research purposes are equally acceptable.

4.8. A small number of embryos used in research have been created specifically for a research project or have been created in the process of specific research projects. However the vast majority of embryos used in research are embryos created in the course of infertility treatment and which, for whatever reason, are no longer required for treatment (see Table 2 – Chapter 3). The only options at this stage are to let the embryos perish or to use them, with the express consent of the individuals whose eggs or sperm have been used to create the embryo, in licensed and controlled research as part of the effort to enhance future fertility treatment and human lives.

4.9. It may be argued that allowing research which involves the extraction of stem cells treats the embryo as no more than a convenient source of research material and thus removes any respect for the embryo as an entity in itself. The moral objection to the use of embryos may increase for some people if embryos were to be produced in a laboratory for the specific purpose of extracting stem cells for experimental purposes, even though the ultimate benefit might be understanding of disease or its treatment. Such an approach,

some would argue, does not retain any sense of the respect for the embryo, used by the Warnock Committee to justify research on embryos.

4.10. A contrary moral view is that, provided the research is necessary to secure benefits to human health in the future, the use of embryos at a very early stage in their development is not lacking in respect. Taking this view, it might be argued that the use of embryos to increase understanding of disease does not differ so fundamentally from the purposes of currently permitted research, even though conceptually the embryo is more closely associated with the reproductive process. In particular, research leading to potential treatments for major diseases of tissue or organs may not be any less respectful of the embryo's moral status than research on congenital disease, for example. Indeed if there is greater potential for the research to benefit a wider range of people or treat a wider range of disorders such research may be more ethically justified.

4.11. The current research purposes specified in the 1990 Act relate only to research which could be envisaged at that time. It is however difficult to argue that they were based on immutable moral criteria. The existence in the 1990 Act of the power to broaden the research purposes in due course supports this view. In all types of embryo research under consideration it has to be accepted that the embryo cannot itself receive any benefit. It is used instrumentally – as a means to an end – and will be destroyed. This is, in any event, an inevitable outcome for all spare embryos which are no longer required for treatment whether or not they are donated for research under the currently allowed research purposes. If the arguments of the Warnock Committee are accepted, the issue to be considered is one of balance: whether the research has the potential to lead to significant health benefits for others, and whether the use of embryos at a very early stage of their development in such research is necessary to realise those benefits. This has been explored in Chapter 2.

4.12. It is not possible to reconcile the opposing views on the moral status of the embryo and on the use of embryos in research. There are those for whom any use of an embryo in such research is morally objectionable and cannot be balanced by the potential benefits. However, those with such a view must be opposed to all research on embryos, not just to these new uses. The Expert Group accepted the 'balancing' approach which commended itself to the majority of the Warnock Committee. On this basis, extending the permitted research uses of embryos appears not to raise new issues of principle. The position encapsulated in the 1990 Act is that it is permissible to undertake research which involves the use (and inevitable destruction) of embryos where there is good reason to believe that such use will lead to improvements in, for example, infertility treatment or the understanding of congenital disease. This reasoning, in the view of the Expert Group, applies equally to research which involves the use of embryos to obtain stem cells to study the development of tissue for potential therapeutic purposes.

The creation of embryos for research

4.13. Some people may distinguish between research to derive stem cells from spare embryos and that involving the creation of embryos specifically for, or in the course of, research. Although only a very small number of embryos have been created specifically in the course of research there are examples of research which could not be conducted using spare embryos. The prime example to date has been where it is necessary to test the viability of sperm or eggs by attempting to create an embryo, for example, as part of the development of new storage or *in vitro* fertilisation techniques.

4.14. For research on the extraction and culture of human embryonic stem cells it may be possible to use spare embryos, particularly as the stem cells extracted should have the ability to renew themselves and provide cell lines for further research. There should be a sufficient supply of spare embryos for such research. It may therefore not be necessary to create new embryos by *in vitro* fertilisation for basic research on the extraction of stem cells. However, it has been concluded in Chapter 2 that the creation of embryos by

cell nuclear replacement would be a necessary avenue of research to investigate the mechanisms for reprogramming adult cells and to establish whether tissue can be developed which is compatible with the intended recipient.

Ethical Implications of Research Using Cell Nuclear Replacement Techniques

4.15. The prospect of creating human embryos using cell nuclear replacement for research appears to raise particular concerns for many people. The use of the term "cloning" by the media when describing this technique has unfortunate connotations conjuring up as it does images of whole people or parts of people being created or of babies being created as a source of spare parts. In fact, as Chapter 2 has described, embryos created by this technique would be grown only to the blastocyst stage for the extraction of stem cells.

4.16. The Warnock Committee made the assumption that the vast majority of embryos used in research would be spare embryos, created in the course of *in vitro* fertilisation treatment, but no longer required for that purpose. The tiny minority of embryos created specifically for research would have been produced by similar techniques (i.e. mixing sperm and egg in the laboratory to achieve fertilisation outside the body). The creation of embryos by means other than by fertilising an egg with sperm was not possible when the issues were debated by the Warnock Committee and in Parliament.

4.17. The use of cell nuclear replacement to produce human embryos may be said to create a new form of early embryo which is genetically virtually identical to the donor of the cell nucleus. This prospect goes further than that contemplated by either the Warnock Committee or Parliament when it debated these issues, although as described above the creation of embryos for research in this way is not ruled out under the 1990 Act provided that the research is for one of the five existing purposes. However, although these embryos differ in the method of their creation, they are undoubtedly human embryonic life, which, given the right conditions, could develop into a human being.

4.18. In the UK embryos created by cell nuclear replacement cannot be implanted because that would correspond to reproductive cloning. However, the creation and use of embryos in this way for research, where there can be no intention of ever implanting them, may appear to some people to deny their human potential and moral status and treat them merely as an object and a source of human tissue. This 'instrumentalisation' of embryos, treating them simply as a means to an end, is unacceptable to many. This includes some in the middle ground of ethical opinion, who may otherwise be sympathetic to the current research uses of embryos and even the broader research uses of spare embryos proposed for the extraction of stem cells to promote further understanding of diseases and possible treatments. Although such people may not regard the embryo as a full person, they are concerned to retain some sense of its uniqueness and special character as a developing human life.

4.19. There is, however, another perspective. For some people, particularly those suffering from the diseases likely to benefit from the treatments that could be developed, the fact that research to create embryos by cell nuclear replacement is a necessary step to understanding how to reprogramme adult cells to produce compatible tissue provides sufficient ethical justification for allowing the research to proceed. Perhaps though the major potential benefit of research to understand how to reprogramme adult cells is that it should eventually obviate the need to create embryos as a source of stem cells.

4.20. Many people fear that permitting the creation of embryos in this way for research is the 'thin end of the wedge' to eventual human reproductive cloning which is almost universally regarded as ethically unacceptable. To implant an embryo created by cell nuclear replacement without a licence from the HFEA is already a criminal offence under the 1990 Act. Given that the HFEA has stated that it will not

issue any such licences, the existing safeguards prevent the possibility of reproductive cloning in the UK. If additional controls were considered necessary, a new Act of Parliament would be required.

New Ethical Issues Raised by Oocyte Nucleus Transfer

4.21. The Human Fertilisation and Embryology Authority and Human Genetics Advisory Commission Report recommended that research using cell nuclear replacement should be extended to include treatment for 'mitochondrial diseases'. As discussed in Chapter 2, these are very serious diseases, which are caused by defects in the woman's egg outside the nucleus. Taking the nucleus from the woman's egg and placing it into an egg from another woman, from which the nucleus has been removed, might provide a possible cure for this defect.

4.22. This is a different type of cell nuclear replacement from that referred to in the previous section because it leads to the production of a new egg which would still need to be fertilised with sperm. It does not lead directly to the production of an embryo. Nevertheless it would, if adopted as a treatment, be intended to produce a healthy baby. Such treatment would not produce an individual genetically identical to anyone else because the modified egg would have to be fertilised by sperm using *in vitro* fertilisation techniques. Ethical objections to this technique on the basis that it is reproductive cloning are therefore unfounded.

4.23. However, concerns have been expressed about whether such treatment would be considered to be a modification of the human genome in which a person's genetic material, DNA, is altered and that alteration is passed on to the next generation. Such modifications are subject to a moratorium in many countries. Oocyte nucleus transfer, if subsequently carried through to the treatment and implantation stage, may raise ethical issues on the basis of it being a modification of the human genome of a relatively modest kind. However, no such ethical barriers exist to undertaking the initial exploratory research.

4.24. Research into oocyte nucleus transfer would be allowed under both current UK legislation and international conventions. The Explanatory Memorandum to the Council of Europe Convention on Human Rights and Biomedicine points out that the Convention allows medical research which aims to introduce genetic modifications in sperm or eggs if they are not used for procreation. This is subject to the research receiving approval from the appropriate ethical or regulatory body in the country concerned.

4.25. Some people have fundamental ethical objections to making genetic modifications which will be passed on to the next generation because they are seen as an unwarranted interference with nature. There is also the very practical objection that it is difficult to predict the long term effects of such modifications. For this reason considerable laboratory based research would be needed before the use of oocyte nucleus transfer in treatment could be considered.

Conclusions

4.26. The Expert Group recognised that the use of embryos in research to extract stem cells raises concerns for some people. Having given careful consideration to the spectrum of ethical opinion, the Expert Group concluded that, as with the currently permitted uses of embryos in research, the potential benefit of the research could be weighed against the respect owed to the embryo given its very early stage of development. The question was, therefore, whether the potential benefit of research involving extracting stem cells from early embryos was sufficient to justify the use of embryos in such research and whether there were alternatives to embryo research offering equivalent benefits.

4.27. The Expert Group concluded that the potential benefit of research involving embryonic stem cells in terms of eventual therapeutic possibilities was equally as valuable as those purposes for which embryo research is currently allowed. Indeed, the ultimate benefit to human health of such research could prove to be of far

wider application and significance. The Expert Group also concluded that there was not, currently, an alternative to research to derive embryonic stem cells which would offer equivalent benefit in the potential to develop tissue for therapeutic uses. In the long term, reprogramming adult cells could be an alternative but research on embryos created by cell nuclear replacement was an essential step towards this goal.

4.28. An extension would be needed to the purposes in the Human Fertilisation and Embryology Act 1990 for which embryos may be used in research, to allow for research to increase understanding about human disease and its cell-based treatments including that involving the extraction and culture of stem cells from embryos. The Expert Group concluded that such an extension should be recommended. Such research would be subject to the controls operated by the Human Fertilisation and Embryology Authority.

4.29. Recognising the sensitivity of this area of research for some people, the Expert Group concluded that it would be important for couples donating their embryos for research to receive a full explanation of the proposed research, including whether the extraction of stem cells was envisaged, before they gave their consent. The Expert Group considered whether a woman donating fetal tissue for research should similarly be required to give specific consent to the use of that tissue for the extraction of stem cells. The Expert Group noted that the principles governing research involving fetal tissue laid down in the Polkinghorne Code of Practice required that the woman should not be informed of the specific use to be made of the fetal tissue. The Expert Group concluded that the Code of Practice should be reviewed to consider whether specific consent to the use of fetal tissue for the extraction of stem cells should be required.

4.30. The creation of embryos by cell nuclear replacement as a source of compatible stem cells raises additional concerns for many people about the creation of embryos as a means to an end and their use as a source of tissue. While recognising the strength of this contrary view, the Expert Group concluded that the "balancing" approach which justified the use of spare embryos created by in vitro fertilisation applied equally to embryos created by cell nuclear replacement.

4.31. Although it is not yet known whether the cell nuclear replacement technique will be successful in creating an early human embryo, the Expert Group concluded that the potential of cell nuclear replacement to provide an understanding of how adult cells might be reprogrammed to behave like unspecialised stem cells again was so important for the eventual development of compatible tissue that research to investigate the feasibility of growing human cells in this way was justified.

4.32. The Expert Group accordingly concluded that the creation of embryos by cell nuclear replacement and their use in research should be allowed for the purposes of increasing understanding about human disease and its cell-based treatments. However, it was important that such research was subject to the rigorous controls operated by the Human Fertilisation and Embryology Authority. In particular, for such research the Authority would need to be satisfied that the creation of an embryo by cell nuclear replacement was necessary for the purposes of the research and that alternatives could not serve the research purposes equally as well.

4.33. The Expert Group noted that its conclusion on the use of embryos (whether created by *in vitro* fertilisation or cell nuclear replacement) in research to increase understanding about human disease and its cell-based treatments was in line with the recommendations of the Nuffield Council on Bioethics, whose report *'Stem cell therapy: the ethical issues'* was published on 6 April 2000.

4.34. The Expert Group noted that any subsequent research involving cultures of stem cells derived from embryos created either by egg and sperm or cell nuclear replacement would not fall within the controls operated by the Human Fertilisation and Embryology Authority or any other body. Given the controls on research involving the extraction of stem cells from embryos, the Expert Group concluded that further scrutiny of individual proposals for subsequent research involving the use of stem cells derived from embryos was unnecessary. However, it would be desirable for the progress of the research to be monitored and that progress assessed to determine whether the potential benefits envisaged were being realised and to highlight any currently unforeseen concerns which may arise.

4.35. The Expert Group recognised that some people had concerns that allowing embryos to be created by cell nuclear replacement for research would increase the likelihood of such embryos being implanted in a woman and used for human reproductive cloning. The Expert Group noted that the implantation of embryos created in this way would be a criminal offence under the Human Fertilisation and Embryology Act 1990, as no implantation can take place without a licence from the Human Fertilisation and Embryology Authority. The Expert Group concluded that the current regulatory controls were sufficient to prevent human reproductive cloning in the UK.

4.36. The Expert Group concluded that, while the possibility of oocyte nucleus transfer for treatment purposes may be regarded as constituting a modest modification of the human genome, research into the technique should be allowed to proceed because of the possible benefit this would offer those suffering from mitochondrial disorders in the long term. Both current UK law and international conventions would allow such basic research. The feasibility and safety of the technique would need to be demonstrated before its use in treatment could be considered.

Chapter 5: Overall Conclusions and Recommendations

This Chapter sets out the overall conclusions of the Expert Group, the Expert Group's recommendations and the suggested means of meeting those recommendations.

5.1. The Expert Group was established following the joint report from the Human Fertilisation and Embryology Authority and Human Genetics Advisory Commission to assess current developments in research involving stem cells and the creation of embryos by cell nuclear replacement, and their potential for developing understanding of and treatments for diseased tissue and organs; to examine the alternatives to such research; to consider the safety and technical issues; and to consider any new ethical issues that might arise.

5.2. As the Expert Group addressed its task it became clear that it was the potential benefits of research involving stem cells that should be the initial focus of its attention. It is the ability to isolate and keep these unspecialised cells in the laboratory and then grow them on into specific tissue types that offers the possibility of new techniques for treatment of disease and injury.

5.3. This potential has been demonstrated in principle in research in animals and the limited work involving adult derived stem cells. While stem cells could be extracted from a number of sources, stem cells derived from embryos currently appear to offer the greatest potential in their ability to self renew and the range of tissues it should be possible to develop from them. Alternative sources of stem cells, especially those from cord blood or from adults could also become important. However the Expert Group concluded that there was not, currently, an alternative to research to derive stem cells from embryos which would offer equivalent benefit.

5.4. The creation of embryos by cell nuclear replacement will be necessary to understanding the mechanism by which an adult cell nucleus could be reprogrammed by an enucleated egg. This could lead in the longer term to techniques being developed to reprogramme adult cells without the need to create an embryo and to overcome the problems of tissue rejection.

5.5. Although the Expert Group recognised that some people were opposed to any research involving human embryos it concluded that the proposed new research uses, to advance understanding of and develop treatments for diseased tissue and organs, did not raise fundamentally different ethical issues from the currently permitted research uses. The Expert Group's view was that the potential benefits of the research justify the use of embryos at a very early stage of their development, including embryos created by cell nuclear replacement, and the research should be permitted.

5.6. However, the Expert Group concluded that such research should only take place under a system of rigorous safeguards. For research using embryos for the proposed new purposes, including research to extract and culture stem cells, such safeguards are provided by the existing system of regulation operated by the Human Fertilisation and Embryology Authority. This requires the Authority to satisfy itself that the use of embryos or the creation of embryos for the purposes of the research project is necessary. It also requires that individuals whose eggs or sperm are used in creating the embryos give specific consent to their use in research. The Expert Group took the view that specific consent should be obtained where the embryos are to be used in research including the extraction of stem cells.

5.7. The Expert Group considered that the progress of the research involving embryonic stem cells should be kept under review to assess whether it is delivering its promise and to identify any unanticipated concerns which might arise.

5.8. The Expert Group considered that research should be undertaken across the range of possible sources of human stem cells and that the Research Councils should give a high priority to such research. The feasibility of establishing banks of stem cell cultures from all these sources should also be considered, initially to facilitate the research and in the longer term to provide a potential resource for the supply of tissue-typed cells for treatment.

5.9. The Expert Group concluded that research to investigate whether the technique of oocyte nucleus replacement offered a possible method of treatment for mitochondrial disease should be pursued. This offers a possible means of helping an affected mother to have a child who inherits her genetic make-up (together with that of her partner) without her damaged mitochondria.

Recommendations

5.10. The Expert Group accordingly makes the following recommendations:

Recommendation 1:

Research using embryos (whether created by *in vitro* fertilisation or cell nuclear replacement) to increase understanding about human disease and disorders and their cell-based treatments should be permitted, subject to the controls in the Human Fertilisation and Embryology Act 1990.

Research using embryos created in the laboratory, either those that are no longer needed for *in vitro* fertilisation treatment or those that are created specifically for research is permitted at present under the Human Fertilisation and Embryology Act 1990 subject to the approval of the Human Fertilisation and Embryology Authority. However, such research is only permitted for certain specified purposes.

Implementing this first recommendation could be achieved by extending (in Regulations) the categories of research permitted by the Human Fertilisation and Embryology Act 1990. Such research would continue to be subject to the existing controls within the 1990 Act including the need for the Human Fertilisation and Embryology Authority to be satisfied on a case by case basis that the proposed use of embryos is necessary for the purposes of the research. In particular, if the research project involves the creation of embryos specifically for the project (rather than the use of embryos no longer needed for *in vitro* fertilisation treatment) the Authority would need to be satisfied that this is justified for the purposes of the particular research project.

The 1990 Act does not distinguish between embryos created from eggs and sperm and those created by combining the nucleus of a cell with an egg which has had its nucleus removed (known as cell nuclear replacement).

Recommendation 2:

In licensing any research using embryos created by cell nuclear replacement, the Human Fertilisation and Embryology Authority should satisfy itself that there are no other means of meeting the objectives of the research.

The extension to the categories of research necessary to give effect to Recommendation 1 would encompass research using embryos created by cell nuclear replacement. However, the Human Fertilisation and Embryology Authority would need to be satisfied for each research application that the creation of embryos in this way and their use is necessary for the purposes of a specific research application. In reaching its decision, the Authority would need to take particular account of progress in animal studies and relevant related work in humans. The Authority would have to be assured that alternatives to cell nuclear replacement have been adequately considered before authorising any such research.

Recommendation 3:

Individuals whose eggs or sperm are used to create the embryos to be used in research should give specific consent indicating whether the resulting embryos could be used in a research project to derive stem cells.

Fully informed consent must be given by individuals whose eggs or sperm are used to create embryos for research under the existing requirements of the Human Fertilisation and Embryology Act 1990. It would be open to the Human Fertilisation and Embryology Authority to specify in a research licence that, in the course of seeking consent, researchers should explain that stem cells would be derived as part of the research and also explain their subsequent intended use. Embryos could only be used in the project if the individuals concerned consented. The Polkinghorne Code of Practice on the Use of Fetuses and Fetal Material in Research and Treatment should be reviewed to consider whether specific consent to the use of fetal tissue for the extraction of stem cells should be required.

Recommendation 4:

Research to increase understanding of, and develop treatments for, mitochondrial diseases using the cell nuclear replacement technique in human eggs, which are subsequently fertilised by human sperm, should be permitted subject to the controls in the Human Fertilisation and Embryology Act 1990.

Research to increase knowledge about mitochondrial disease would fall within the five research purposes currently permitted under the Human Fertilisation and Embryology Act 1990, as it would be for the purpose of increasing knowledge about the causes of congenital disease. However, to allow for research into possible treatments for mitochondrial disease, the categories of research permitted by the Act would need to be extended (in Regulations), as for Recommendation 1.

Recommendation 5:

The progress of research involving stem cells which have been derived from embryonic sources should be monitored by an appropriate body to establish whether the research is delivering the anticipated benefits and to identify any concerns which may arise.

If the earlier recommendations are implemented, the Human Fertilisation and Embryology Authority would be responsible for licensing research projects involving the use of embryos for the extraction of stem cells. The Human Fertilisation and Embryology Authority might be charged jointly with the Human Genetics Commission to keep under review information on the progress of stem cell research as a basis for advising Ministers from time to time on developments in human embryonic stem cell research, the implications for health and health care, and any unforeseen concerns which may arise.

Recommendation 6:

The mixing of human adult (somatic) cells with the live eggs of any animal species should not be permitted.

The Human Fertilisation and Embryology Act 1990 controls the circumstances in which human eggs or sperm can be mixed with the live eggs or sperm of any animal. These circumstances are primarily limited to testing the fertility or normality of human sperm. The 1990 Act does not control the mixing of animal eggs with other human cells. A new Act of Parliament would be required to implement this recommendation. In the meantime bodies funding research may wish to make a declaration that they would not fund or support research involving the creation of such hybrids.

Recommendation 7:

The transfer of an embryo created by cell nuclear replacement into the uterus of a woman (so called 'reproductive cloning') should remain a criminal offence.

The creation of a human embryo by cell nuclear replacement is governed by the Human Fertilisation and Embryology Act 1990 in the same way as the creation of embryos in the laboratory from eggs and sperm. The Human Fertilisation and Embryology Authority has made it clear that it will not license treatment which involves transferring an embryo created by cell nuclear replacement into the womb of a woman. To undertake such a procedure without a licence from the Authority is currently a criminal offence. If the protection provided by the Human Fertilisation and Embryology Act 1990 were not found to be sufficient in the future then additional controls would require a new Act of Parliament.

Recommendation 8:

The need for legislation to permit the use of embryo-derived cells in treatments developed from this new research should be kept under review.

If the previous recommendations are implemented and the research is successful, the time may come when clinical scientists will wish to apply the results of research for the benefit of patients. The only treatments using embryos created outside the human body which the Human Fertilisation and Embryology Authority can currently license are those intended to help a woman become pregnant. A new Act of Parliament would be needed to allow the creation of embryos to derive cells for other types of treatment. The assessment of the progress of research involving stem cells derived from embryonic sources by the body proposed at Recommendation 5 would enable it to advise Ministers in due course on the need for new legislation.

Recommendation 9:

The Research Councils should be encouraged to establish a programme for stem cell research and to consider the feasibility of establishing collections of stem cells for research use.

The Department of Health should seek to encourage Research Councils to give high priority to this research through its Concordats with them. Research programmes might focus on the derivation of cell lines from embryonic tissue and other sources, the production of stem cell lines by cell nuclear replacement, reprogramming the somatic cell nucleus to derive stem cell lines and the differentiation of stem cell lines for therapeutic purposes. Encouragement should be given to research teams in the public and private sectors who propose to work jointly on these problems. The establishment of collections of stem cell cultures would provide a valuable source of ethically obtained cultures for researchers which would avoid the need to import cell lines.

Chief Medical Officer's Expert Group on Therapeutic Cloning

Terms of Reference:

- to establish the extent to which there is a current research focus on therapeutic cloning including stem cell studies, when developments are likely to arise and where they could lead;
- to assess the anticipated benefits of such research; the potential risks; and any alternative approaches that might be pursued to achieve the same benefits;
- in the light of the assessed benefits, risks and alternatives to consider whether there are any ethical and social implications beyond those addressed by the HFEA/HGAC Report, *Cloning Issues in Reproduction, Science and Medicine;*
- to advise whether regulations need to be made under the Human Fertilisation and Embryology Act 1990 to extend the purposes for which the Human Fertilisation and Embryology Authority may issue licences for research involving human embryos;
- to advise on whether any additional regulation of the use of embryonic cell lines (such as stem cells) is required.

Membership:

Professor Liam Donaldson	Chief Medical Officer, (Chair).
Professor David Baird	MRC Clinical Research Professor, Centre for Reproductive Biology, University of Edinburgh.
Professor W F Blakemore	Department of Clinical Veterinary Medicine, University of Cambridge.
Professor John Burn	Regional Genetics Services, Newcastle upon Tyne; member of the Human Genetics Commission.
Professor Alastair Campbell	Professor of Ethics in Medicine, University of Bristol.
Professor Dian Donnai	CMO's Consultant Advisor in Genetics, Regional Genetics Services, Manchester.
Professor Martin Evans	Director and Professor of Mammalian Genetics, Cardiff School of Biosciences, Cardiff University.
Professor Brian Heap	Master of St Edmund's College, Cambridge.
Professor David Linch	Department of Haematology, University College London.
Sir Robert May	Government's Chief Scientific Adviser.
Professor Sir Peter Morris	Nuffield Professor of Surgery, Oxford University.

Mr Derek Morgan	Reader in Law, Cardiff University.
The Revd Dr John Polkinghorne	Member of the Human Genetics Commission; Chairman of the former Advisory Committee on Genetic Testing; member of the former Human Genetics Advisory Commission.
Sir David Weatherall	Honorary Director, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford.

ANNEX B

Letter from the Chief Medical Officer on the Expert Advisory Group on Therapeutic Cloning in Humans (2 September 1999)

1. The UK Government has announced that it wishes to establish the extent to which there is an identified need for and interest in research on human embryos and involving cloning techniques for therapeutic purposes. I have been asked as the Government's Chief Medical Officer to establish an expert advisory group to seek views widely on these questions and to establish more clearly the evidence of potential benefits for human health of such research.

2. I am writing to invite your views on the questions that follow to assist the group in their deliberations.

3. As background – you will know that a report from the UK Human Genetics Advisory Commission (HGAC) and Human Fertilisation and Embryology Authority (HFEA) ("Cloning: Issues in Reproductive Science and Medicine") available at www.dti.gov.uk/hgac published in December 1998 recommended that the purposes for which human embryos maybe used in research under UK legislation should be extended to include research to develop methods of therapy for:

   - mitochondrial diseases;
   - diseased or damaged tissues or organs.

   These were envisaged to be the main applications of cell nuclear replacement techniques which the report described as "therapeutic cloning", although I recognise that other areas may also be of interest.

4. To help the expert group I would welcome your views on:

   - what are the current research areas on therapeutic cloning, including stem cell studies, and which are the most important?
   - the areas of human health in which the use of therapeutic cloning techniques is most likely to provide benefits?
   - how close are we to being able to replicate animal work in humans?
   - what are the technical problems which might arise?
   - are you aware of any safety issues?
   - are there alternatives to research on human embryos, created in vitro, to achieve the same ends? If so, is it likely that they will be available within the next five years?
   - what are the ethical and social implications of such research and its potential therapeutic application?
   - what would be the likely future consequences of the development of therapeutic cloning technology for health care provision?
   - any other comments you wish to make?

5. While we will be reviewing the published research please draw my attention to any work you think is particularly relevant. And please indicate if there are implications from any work you are currently undertaking in related areas, that you would be prepared to share with me on a confidential basis.

6. I should emphasise that human reproductive cloning which cannot take place under UK law is not within the scope of this exercise, nor is the expert group being asked to revisit the report of the HGAC/HFEA except in regard to developments that have occurred since 1998.

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