

Stem Cell Therapy: the ethical issues

a discussion paper

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28 Bedford Square
London WC1B 3EG**

**Telephone: 020 7681 9619
Fax: 020 7637 1712
Email: bioethics@nuffieldfoundation.org
Website: <http://www.nuffieldfoundation.org/bioethics>**

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Professor Ian Kennedy (*Chairman*)

Professor Martin Bobrow CBE (*Deputy Chairman*)

Professor Tom Baldwin

Professor Sir Kenneth Calman KCB FRSE*

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Lady Hornby

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Professor Albert Weale FBA

* *(co-opted member of Council for the period of his Chairmanship of the Working Party on the ethics of healthcare-related research in developing countries)*

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- 1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;
- 2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;
- 3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

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**Attendees of the Round Table meeting on
Stem Cell Therapy: the ethical issues**

Professor Martin Bobrow CBE, Department of Medical Genetics,
Cambridge Institute for Medical Research and Deputy Chairman of
Nuffield Council on Bioethics

Professor Tom Baldwin, Department of Philosophy, University of York,
member of Nuffield Council on Bioethics

Lady Hornby, Chairman of The Kingwood Trust, member of Nuffield
Council on Bioethics

Professor Alexander McCall-Smith, Faculty of Law, University of
Edinburgh

Dr Anne McLaren DBE FRS, Wellcome/CRC Institute Cambridge, member
of the Nuffield Council on Bioethics

Secretariat

Dr Sandy Thomas (Director)

Ms Susan Bull

Ms Julia Fox

Ms Yvonne Melia

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Executive Summary

The ability to culture human stem cells long term, and possibly indefinitely, and to control how such cells specialise to form the different tissues of the body offers the possibility of major advances in healthcare. Stem cells have been isolated and cultured, but a great deal of research is required to develop cell lines which can generate replacement cells and tissues to treat many diseases. The use of human pluripotent stem cells is controversial primarily because much of the current research is focused on deriving these cells from human embryos and cadaveric fetal tissue. We have examined the ethical issues raised by the potential of stem cells derived from donated embryos, embryos created specifically for research purposes, cadaveric fetal tissue and somatic cell nuclear transfer (SCNT).

We conclude that the removal and cultivation of cells from a donated embryo does not indicate lack of respect for the embryo. We take the view that there are no grounds for making a moral distinction between research into diagnostic methods or reproduction which is permitted under UK legislation and research into potential therapies which is not permitted. **We therefore recommend that research involving human embryos be permitted for the purpose of developing tissues to treat diseases from derived embryonic stem (ES) cells and that Schedule 2 of the Human Fertilisation and Embryology Act be amended accordingly.** As long as there are sufficient and appropriate donated embryos from IVF treatments for use in research, the Council takes the view that there are no compelling reasons to allow additional embryos to be created merely to increase the number of embryos available for ES cell research or therapy. However, we suggest that this issue be kept under review.

We conclude that the code of practice set out in the Polkinghorne Review provides an adequate framework for the use of fetal tissue in the derivation of embryonic germ (EG) cells. We suggest, however, that the question of consent for the use of donated fetal tissue for the purpose of deriving EG stem cells be re-considered in the context of the current guidance and regulation. While we recommend that research be permitted, **we also recommend that as a safeguard to protect all embryo donors who could theoretically be identified by analysis of DNA of an ES cell line, they be specifically asked to consent to this research and any subsequent use of the cell line.**

We consider that research into SCNT and other forms of reprogramming the nuclei of human somatic cells may potentially offer very significant medical benefits. Where such research falls within the remit of the HFE Act, adoption of the amendment to Schedule 2 recommended above would permit such research to be licensed. We understand that a possible objection to this is that it could prepare the ground for reproductive cloning. However, reproductive cloning (which has the intention of

producing a new individual who is genetically identical to the nuclear donor) is not permissible under UK law; the purpose of this proposed use of SCNT, by contrast, is to allow research into means of producing stem cells for cell and tissue therapy.

Introduction

- 1 There is great interest worldwide in discovering and developing a permanent source of tissues which would be capable of generating any cell type and which would avoid the problem of transplant rejection. Scientists have recently begun isolating and culturing human pluripotent stem cells, i.e. those cells which have an unlimited capacity to divide and the potential ability to develop into most of the specialised cells or tissues of the body. In July 1999, the Nuffield Council on Bioethics decided to hold a Round Table meeting to consider the ethical issues raised by human stem cell research. This discussion paper is based on that meeting, which took place in September. A draft of the paper was presented to the Chief Medical Officer's (CMO) Expert Advisory Group on Therapeutic Cloning in November.¹
- 2 Recent research suggests that human stem cells can give rise to many different types of cells, such as muscle cells, nerve cells, heart cells, blood cells and others. They raise the possibility, therefore, of major advances in healthcare. For example, stem cells could be used to generate replacement cells and tissues to treat many diseases and conditions, including Parkinson's disease, Alzheimer's disease, leukaemia, stroke, heart disease, diabetes, multiple sclerosis, rheumatoid arthritis, spinal cord injury and skin conditions, including burns.² The availability of stem cells may also change the way that drugs are tested. New drugs could be tested for safety and efficacy on cultured liver or skin cells derived from stem cells before being tested on humans. Further research on stem cells also promises to improve our understanding of the complexities of normal human development.
- 3 Stem cells have the capacity to multiply indefinitely. They can give rise to new stem cells with the same potential and more specialised

¹ In December 1998 the Human Genetics Advisory Commission (HGAC) and Human Fertilisation and Embryology Authority (HFEA) published a joint report entitled **Cloning Issues in Reproduction, Science and Medicine**. The UK Government responded by asking the CMO to establish an expert advisory group to examine therapeutic cloning in humans. Once established, the CMO's expert advisory group invited submissions on therapeutic cloning.

² Clinicians may not, however, be able to cultivate these cells to the sophisticated level of organisation that is required for the formation of entire organs, such as the heart. Xenografts currently offer one hope of providing organs for transplantation.

daughter cells. This unique property could allow the creation of tissue banks of both undifferentiated and specialised cells and tissues. Treatment of diseased and damaged tissue would involve transplanting new cells or tissue of the type affected by the particular disease, such as cardiac cells in the case of heart disease, into the patient. In recent animal research, stem cells injected into the heart were incorporated into the heart muscle and were found to beat in synchrony with the host heart.

- 4 Different forms of stem cells retain varying abilities to differentiate into specialised tissues. *Multipotent* stem cells, i.e. cells which can be multiplied and maintained in culture but do not have an unlimited capacity for renewal, can be derived from fetuses and are present throughout life but in progressively decreasing numbers in adults. Research has attempted to determine whether multipotent stem cells of a specific type (such as neural cells) could be differentiated into another type of stem cell. Although recent research has reported that neural stem cells injected into mouse blood could give rise to blood stem cells, this finding has yet to be confirmed. Other research on multipotent stem cells transplanted into the 'shiverer' mouse model of multiple sclerosis demonstrated that these cells could differentiate to form the neural glial cells, which are absent in multiple sclerosis sufferers. The use of fetal stem cell lines could reduce the amount of fetal tissue currently used in therapy. For example, instead of the neural tissue from six fetuses being required to treat one patient with Parkinson's disease, the neural stem cells from one fetus could be used to establish a stem cell line which could offer the possibility of treating many patients.
- 5 *Pluripotent* stem cells have the potential to give rise to any cells of an adult animal.³ When these cells are derived from an embryo, they are termed embryonic stem (ES) cells. When they are derived from primordial germ cells in a fetus (the region that is destined to develop into the sperm or eggs), they are called embryonic germ (EG) cells. Research is currently focused on ES cells because attempts to derive all forms of adult cells from EG cells in mice have led to abnormalities. *Totipotent* cells, according to one definition, can differentiate into every kind of cell line found in a developing embryo, and hence could, on their own, develop into an

³ Pluripotent stem cells are derived from the blastocyst (or ball of cells) formed in early embryonic development. These stem cells cannot develop on their own into an entire animal because at this embryonic stage the outer and some of the internal cells of the blastocyst have already become differentiated. The pluripotent stem cells are therefore unable to give rise to tissues, such as the placenta, which are essential for an embryo to develop.

embryo.⁴ An alternative definition equates totipotent with pluripotent cells, which cannot by themselves generate embryos.

- 6 Research to establish cell lines which can replicate indefinitely currently uses ES and EG cells derived from embryos and fetuses respectively. Six to eight pluripotent cell lines have been developed in the US and Singapore. None are yet established in the UK. As progress in research is expected to lead to the establishment of stem cell banks, the need for embryonic and fetal tissue should diminish as the stem cell lines will be self-replicating.
- 7 The potential scope of this technology and the range of its applications are very wide. The first developments are likely to be the creation of tissue banks of undifferentiated and differentiated cells and tissues for transplantation. As with organ transplants, the use of these cells will also lead to transplant rejection. The degree of rejection will depend on the type of tissue transplanted: neural stem cells are protected to some extent because of the brain's unique immunological status. In the case of muscle, skin and pancreatic cells, rejection will be more of a problem. Immunosuppressive drugs could be used but in the long-term these may contribute to increased risk of infection and cancer. Transplanted cells can be encapsulated to prevent attack from host cells, as for example, in the case of pancreatic cell grafts where insulin can be released while the cell graft is protected. Such an approach will not always be feasible. For example, heart cells need to be attached to the heart tissue and to beat in synchrony with it. A potential solution to the problem of cell transplant rejection is the development of very comprehensive pluripotent stem cell collections that are comprised of cells compatible with almost any transplant recipient. However, there are very many different immunological genotypes.
- 8 It has also been proposed that the nucleus of a donated oocyte⁵ could be removed and replaced with the nucleus of a somatic cell from a patient. This is called somatic cell nuclear transfer (SCNT). In animals, embryos formed by SCNT can, in a small proportion of cases, undergo normal development. If it proves possible in the human to create a blastocyst⁶ *in vitro* by SCNT, any pluripotent stem cells cultivated from the resulting embryo would be

⁴ Totipotent stem cells are defined in two ways: either as cells capable of giving rise individually to an entire adult organism or as cells which give rise to every cell line in the developing fetus. According to the former definition, they exist for a short period of embryonic development, probably only up to the 2-4 cell stage in humans.

⁵ An oocyte is also known as an 'egg' and is the female germ cell.

⁶ A blastocyst is a hollow ball of cells which develops about five days after fertilisation of the egg at a stage before implantation in the wall of the uterus. The outer layer of the blastocyst's cells go on to form the placenta, while the inner cells form the embryo and its membranes.

genetically almost identical to the patient and, if injected, would not stimulate immune rejection. Although the formation of these cells would necessitate the creation of an embryo, once it has been determined how the oocyte reprogrammes adult somatic nuclei, researchers may be able to create pluripotent cell lines directly from patients, circumventing the embryo stage. This approach still requires a good deal of further research before it can be considered a serious option.⁷

Regulation in the UK

9 In the UK any research into human embryos is governed by the Human Fertilisation and Embryology Act (1990) (HFE Act). The uses of fetal tissue, from which EG cells could be derived, are subject to guidance set out in the Polkinghorne Review (1989).⁸ The development and use of cell lines are the subject of health and safety regulation and good practice guidance. In the next section, we discuss the provisions concerning:

- i) the use of embryos
- ii) the use of fetuses
- iii) somatic cell nuclear transfer
- iv) stem cell lines.

The use of embryos

10 The Human Fertilisation and Embryology Authority (HFEA) is a statutory regulatory body established through the HFE Act. The HFEA's principal tasks are to license and monitor clinics carrying out *in vitro* fertilisation, donor insemination and human embryo research. The HFE Act permits licensed research on human embryos of up to 14 days of development.⁹ Under the terms of the HFE Act, it is a criminal offence to carry out any treatment using human embryos outside the body, to use donated gametes, to store any oocytes, sperm or embryos, or to undertake any research on human embryos without a licence from the HFEA. As the establishment of ES cell lines requires research on human embryos, it is governed by the Act.

⁷ The Royal Society (2000) **Therapeutic Cloning: A submission by the Royal Society to the Chief Medical Officer's Expert Group**, The Royal Society, London.

⁸ Committee to Review the Guidance on the Research Use of Fetuses and Fetal Material (1989) **Review of the Guidance on the Research Use of Fetuses and Fetal Material**, HMSO, London.

⁹ The 14 day stage immediately precedes the primitive streak stage at which both the development of individual embryos and cell determination for the future fetus are established.

11 The derivation of a pluripotent stem cell from a donated blastocyst or the creation of an embryo for research purposes, like all other human embryo research, requires a licence from the HFEA.¹⁰ However, Schedule 2 of the HFE Act states that the HFEA cannot license any research unless it appears to the Authority to be necessary or desirable for one of the following purposes:

- a) *promoting advances in the treatment of infertility,*
 - b) *increasing knowledge about the causes of congenital disease,*
 - c) *increasing knowledge about the causes of miscarriage,*
 - d) *developing more effective techniques of contraception, or*
 - e) *developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation,*
- or such other purposes as may be specified in regulations by the Secretary of State.*¹¹

12 The therapeutic use of stem cells was not envisaged when the Act was drafted and no specific provision has been made for it. A regulation to permit research aimed at the derivation of ES cells for therapeutic use would need to be laid before Parliament but would not require a change in primary legislation. The report from the HFEA and the Human Genetics Advisory Commission (HGAC)¹² recommended that the Secretary of State should consider adding two further purposes to the list of purposes outlined above in Schedule 2:

- *developing methods of therapy for mitochondrial diseases;*¹³

¹⁰ Licences to derive stem cells from blastocysts have been given for research into the treatment of infertility, to examine the culture of embryos to the blastocyst stage and then to attempt to derive stem cells, in order to develop improved culture conditions and assess the developmental potential of such blastocysts. Licences have also been granted for the creation of embryos for specific research purposes, for example where the aim is to determine whether unfertilised oocytes can be safely frozen and for research into the development of embryos where an oocyte has been fertilised by immature sperm via intracytoplasmic sperm injection (ICSI).

¹¹ In this respect, the Secretary of State's powers are limited by paragraph 3(3) of Schedule 2.

¹² Human Genetics Advisory Commission and Human Fertilisation and Embryology Authority (1998) **Cloning Issues in Reproduction, Science and Medicine**, Department of Trade and Industry, London.

¹³ Mitochondrial diseases are due to mutations in mitochondrial DNA (deoxyribonucleic acid) rather than nuclear DNA. Because mitochondria are inherited exclusively from females, these diseases show maternal inheritance.

- *developing methods of therapy for diseased or damaged tissues or organs.*

The use of fetuses

- 13 In the UK there are no specific statutory provisions governing the use that can be made of tissues from the cadavers of fetuses, although the Abortion Act (1967) governs the legality of the abortion which makes fetal tissue available. Any subsequent use of fetal tissue was considered in 1989 by the Polkinghorne Committee which reviewed the guidance on the research use of fetuses and fetal material and recommended a code of practice.¹⁴ The uses of fetal tissue contemplated in the Review included teaching, therapy and research. The Polkinghorne Review concluded that 'ethics committees should examine all proposals for work with fetuses or fetal tissue, whether alive or dead, and whether classed as research or therapy, because of the high level of public concern'. Research ethics committees in the UK have already approved research on the technique of transplanting cadaveric fetal tissue into the brains of those affected with Parkinson's disease.

Somatic cell nuclear transfer

- 14 One way to avoid transplant rejection of cells or tissues derived from somatic cells would be to use stem cells which are derived from the patient's own cells (see paragraph 8). This would involve placing the nucleus from a somatic cell of a patient into an enucleated oocyte. The oocyte would then be cultured to the blastocyst stage and stem cells used to initiate a cell line. The HFE Act expressly prohibits one type of cloning, that involving 'replacing the nucleus of a cell of an embryo with a nucleus taken from a cell of any person'. However, the technique being contemplated above involves nuclear substitution into an egg and not an embryo, and thus is not specifically covered by the prohibition of cloning in the Act.
- 15 Ministers and the HFEA are, nevertheless, content that the HFE Act allows the HFEA to regulate nuclear replacement into unfertilised eggs through its licensing system.¹⁵ Such research, which would require a licence, would be permissible under the additional purposes proposed in the HFEA/HGAC Report, if it were thought to be 'necessary and desirable'. Although HFEA members have agreed that this kind of research, as long as it had a non-reproductive aim,

¹⁴ **Review of the Guidance on the Research Use of Fetuses and Fetal Material** (1989) (Cm 762) Her Majesty's Stationery Office, London.

¹⁵ Human Genetics Advisory Commission and Human Fertilisation and Embryology Authority (1998) **Cloning Issues in Reproduction, Science and Medicine** Department of Trade and Industry, London, paragraph 3.4.

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would be considered,¹⁶ the Report states that 'research applications involving the nuclear replacement of eggs are likely to be some way off for a variety of reasons. In line with general HFEA policy, further research using animal embryos is needed before the use of human embryos would be appropriate.'

Stem cell lines

- 16 What happens once a stem cell line has been established? The Department of Health and other organisations such as the Medical Research Council and UK Co-ordinating Committee on Cancer Research have developed guidelines for their researchers and for others using their cell lines. Derived pluripotent stem cells imported into or developed in the UK would be covered by these guidelines and the health and safety regulations which apply to established cell lines. Where research on such cells involves NHS patients, records, specimens or premises, it would require approval from research ethics committees.

The ethical issues

- 17 The use of human ES cells and EG cells raises important ethical issues which are primarily concerned with the origin of the cells and the way in which they are derived. The fact that these cells currently involve the use of human embryos and cadaveric fetal tissue means that careful examination of the ethical issues is necessary prior to the progress of research in this field. There has been a longrunning and serious debate in the UK and elsewhere about the morality of research on human embryos and elective abortion. Although both are permissible in the UK under certain conditions, this does not preclude further moral debate, and there are widely differing views about the ethical issues raised by such research. However, in considering the ethical issues raised by the use of stem cells we have focused on issues which are additional to those already addressed by UK legislation and guidance.
- 18 Many of the questions posed by embryo research are addressed by the Warnock Report, published in 1984,¹⁷ the HFE Act and the subsequent deliberations of the HFEA. We consider the ethical issues in relation to the sources of stem cells, including embryos arising from infertility treatments, embryos created specifically for research purposes, cadaveric fetal tissue and somatic cell nuclear transfer.

¹⁶ Human Genetics Advisory Commission and Human Fertilisation and Embryology Authority (1998) **Cloning Issues in Reproduction, Science and Medicine** Department of Trade and Industry, London, paragraph 3.9.

¹⁷ **Report of the Committee of Inquiry into Human Fertilisation and Embryology** (1984) (Cm9314), Her Majesty's Stationery Office, London.

The use of donated embryos to produce ES cells

- 19 The debate about the moral status of the human embryo has focused on the question of whether the embryo should be treated as a person, or, at least, a potential person. If the embryo is so considered, then it will be morally impermissible to use it merely as a means to an end, rather than as an end in itself. This would preclude both embryo research and any other procedure not directed to the benefit of that actual embryo. The removal of cells from an embryo would therefore not be morally permissible, regardless of whether these cells were to be used for the benefit of some other person.
- 20 This issue was discussed extensively prior to the passing of the HFE Act. Parliament accepted that embryo research is morally acceptable for specific purposes provided that it is limited to the fourteen days following fertilisation and provided that no embryo which is subjected to research procedures is re-implanted in the uterus. It did not, however, express a view on the moral legitimacy of cultivating cells from embryos and using them for therapeutic purposes.
- 21 A donated embryo has been created with a view to implantation in the uterus. Once it is not implanted, it no longer has a future and, in the normal course of events, it will be allowed to perish or be donated for research. We consider that the removal and cultivation of cells from such an embryo does not indicate lack of respect for the embryo. Indeed, such a process could be regarded as being analogous to tissue donation.
- 22 It is likely to be some time before therapies based on the development of ES cells are established. Before that time is reached, further research will be necessary, and this, of course, will be a form of embryo research. Embryo research is allowed by the HFE Act, but only for those purposes set out in the legislation. These purposes include research into diagnostic methods and reproduction, and do not cover research into therapies (paragraphs 9-11). In our view, however, there are no grounds for making a moral distinction between these two forms of research. Research into potential therapies is not qualitatively different from research into diagnostic methods or reproduction. Neither benefits the embryo upon which research is conducted but both may be of benefit to people in the future. Each form of research involves using the embryo as a means to an end but, since we accept the morality of doing so in relation to currently authorised embryo research, there seems to be no good reason to disallow research on the embryo where the aim of the research is to develop therapies for others. **We therefore recommend that research involving human**

embryos be permitted for the purpose of developing tissue therapies from the derived ES cells and that Schedule 2 of the HFE Act be amended accordingly. The establishment of cell lines may make it unnecessary for donated embryos to be used in this way. This suggests that the moral question may be a 'transitional' one, although there may well be moral issues surrounding the use made of such cell lines. We address this point below.

Consent

- 23 In the UK, couples undergoing fertility treatment must specify the uses which can be made of embryos created from their gametes, including whether or not the embryos can be used in any research project. Schedule 3 of the HFE Act sets out the conditions which must be met for such a consent to be effective. The Schedule requires that couples 'must be given a suitable opportunity to receive proper counselling about the implications of taking the proposed steps' and that they 'must be provided with such relevant information as is proper'.
- 24 In practice, the provision of information given to potential donors varies between clinics in the UK. Some clinics provide general guidance on the type of research work in which embryos are used (see the five permissible categories set out earlier in Schedule 2 of the HFE Act). In contrast, clinics which perform research in their own units may provide information leaflets explicitly outlining the research project in which the embryo will be used and the purposes and objectives of such research. Other clinics provide details of two to three projects in which the embryo might be used and couples can choose to consent to specific projects.¹⁸
- 25 We consider that the use of embryonic tissue in research projects to establish ES cell lines raises issues relating to consent that are different from those raised by other forms of research permissible under Schedule 2 of the HFE Act. Although the establishment of a cell line will involve the destruction of the embryo, the DNA (deoxyribonucleic acid) in the cell of the embryo has the potential to exist indefinitely in culture. The cells could be ultimately used in a wide range of therapeutic applications and, with DNA testing, such a cell line could theoretically be traced back to the individual embryo donors. The theoretical potential to trace the source of a cell line is not unique to ES cells, but applies to any cell line established from donated tissue. Consequently, where specific research regarding the establishment of an ES cell line is contemplated, embryo donors should be asked explicitly whether or not they consent to such research and subsequent use of the cell

¹⁸ M Wall (1999) Inspector Co-ordinator, HFEA. Personal communication.

line.¹⁹ We endorse the recommendations of the US National Bioethics Advisory Commission (NBAC) Report (1999) that:

During the presentation about potential research use of embryos ... the person seeking the donation should:

- *disclose that the ES cell research is not intended to provide medical benefit to embryo donors;*
- *make clear that consenting or refusing to donate embryos to research will not affect the quality of any future care provided to prospective donors;*
- *describe the general area of the research to be carried out with the embryos and the specific research protocol, if known;*
- *disclose the source of funding and expected commercial benefits of the research with the embryos, if known;*
- *make clear that embryos used in research will not be transferred to any women's uterus, and*
- *make clear that the research will involve the destruction of the embryos.*²⁰

*Researchers may not promise donors that ES cells derived from their embryos will be used to treat patient-subjects specified by the donors.*²¹

The creation of embryos to produce ES cells

26 The fact that ES cells potentially have valuable applications in a wide range of diseases raises the question of whether increased demand might lead to the creation of embryos specifically for research which has the purpose of obtaining ES cells and creating immortalised cell lines. Such a development might be seen as a step towards commodification of the embryo and one that denies the embryo the respect it should be accorded. In the UK, the creation of embryos is already permitted for the specific research

¹⁹ We note that not all people wishing to donate embryos need be invited to donate them for the purpose of creating immortal stem cell lines as only very few embryos donated for research would actually be needed for such a purpose.

²⁰ National Bioethics Advisory Commission (1999) **Ethical Issues in Human Stem Cell Research: Volume I**, National Bioethics Advisory Commission, Maryland, USA, Recommendation 5.

²¹ National Bioethics Advisory Commission (1999) **Ethical Issues in Human Stem Cell Research: Volume I**, National Bioethics Advisory Commission, Maryland, USA, Recommendation 6.

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purposes set out in Schedule 2 of the HFE Act. Licences for the creation of embryos have been issued for research, for example on the storage of unfertilised oocytes and the intracytoplasmic sperm injection (ICSI) technique.

- 27 Is there an ethical distinction to be made between the use of a donated embryo for the derivation of ES cells and the use of an embryo created for this purpose? A donated embryo will have been created for use in a reproductive technology programme where the goal is a successful pregnancy. If it is unsuitable or intended to be discarded, its use for the derivation of ES cells will not alter its final disposition. Alternatively, embryos could be created through *in vitro* fertilisation (IVF) from donated gametes with the sole purpose of producing cell lines. Some would argue that such an instrumental use, where the embryo is essentially a means to an end, does not accord with the respect owed to a potential human life. We note, however, that the creation of embryos for specific research is already permissible under the HFE Act if the project cannot be carried out on donated embryos. While there are sufficient and appropriate donated embryos from IVF treatments for use in research, we consider that there are no compelling reasons to allow additional embryos to be created merely to increase the number of embryos available for ES cell research or therapy. However, we suggest that this issue be kept under review.

The derivation of EG cells from cadaveric fetal tissue

- 28 The ethical acceptability of using fetal tissue for the derivation of EG cells is closely tied to the ethical acceptability of abortion. Many of the ethical questions posed by the use of cadaveric fetal tissue were considered by the Polkinghorne Committee in 1989. The Polkinghorne Code of Practice concerning the responsible use of aborted fetal tissue is already in place. Does the use of such tissue for the derivation of EG cells raise additional ethical questions which might require further safeguards? Unlike embryonic tissue, cadaveric fetal tissue is currently used for therapeutic as well as research purposes. The derivation of EG cells and their use would not require a special licence from a statutory body but would be regulated by research ethics committees, which have already approved the use of cadaveric fetal tissue in Parkinson's patients.
- 29 The potential of EG cells to create valuable cell lines for transplantation raises the possibility that an abortion could be sought with a view to donating cadaveric fetal tissue in return for possible financial or therapeutic benefits. The Polkinghorne

Review²² sets out guidance relating to the use of fetal tissue in teaching, research and therapy. In the Review, concerns that knowledge of the use to which fetal tissue could be put might influence a woman's decision to have her pregnancy terminated are discussed. Accordingly, the Review recommended that great care should be taken to separate the decisions relating to abortion and to the subsequent use of fetal material. In addition, it recommended that procedures be implemented which make it impossible for a woman to specify that fetal tissue which she makes available will be used in a particular way. This was intended to limit the degree to which any morally dubious desires could be implemented, and in particular, any ethically unacceptable use of the fetus.

- 30 The Polkinghorne Code of Practice requires that written consent must be obtained from women for use of the fetus or fetal tissue. The process of consent requires 'the mother to be counselled and given all the information, in a form that is comprehensible, to enable her to make a proper judgement of whether or not to allow the fetus to be used for research and therapy.' The Polkinghorne Review recognises that some women may be prepared to consent to some uses of fetal tissue but not others. In contrast to the regulations under the HFE Act governing embryo donation, it concludes 'that to allow for such preferences would be too great a breach of our principle that a mother should not be able to direct that the fetus be used in a specific way'. As a result, it requires that explicit consent for all permissible purposes should be obtained on all occasions.²³
- 31 The NBAC Report goes even further. To ensure that inappropriate incentives do not enter into a woman's decision to request an abortion, the NBAC recommends that directed donation of cadaveric fetal tissue for EG cell derivation be prohibited. It goes on to state that although potential donors of cadaveric fetal material would not receive a direct therapeutic incentive to produce or abort tissue for research purposes in the same way that such personal interest might arise in a transplant context, a prohibition was

²² Committee to Review the Guidance on the Research Use of Fetuses and Fetal Material (1989) **Review of the Guidance on the Research Use of Fetuses and Fetal Material**, HMSO, London.

²³ The Review states that any consent would need to take account of the following:

- *No specific reference should be made to any particular research or therapy nor any suggestion made that any use will, in fact, take place. It should be confirmed that any use will be strictly controlled and restricted to purposes for which tissue of this kind is necessary for medical benefit.*
- *The mother should be assured that appropriate measures will be taken to prevent her being identified by anyone, apart from those attending her...*
- *The mother's explicit consent must be obtained to the use of fetal tissue in research, therapy and teaching.*
- *The mother should be asked to relinquish any property rights.*

thought necessary to ensure that inappropriate incentives, however remote, do not enter into a woman's decision to have an abortion.

32 We do not consider that concerns about inappropriate incentives resulting from a potential benefit deriving from the establishment of an EG cell line are so great that the donation of fetal tissue for such purposes should be prohibited. We suggest that the provisions in the Polkinghorne Review designed to separate the decision to have an abortion and the decision about any use which can be made of the fetal material are sufficient to meet such concerns. Despite concerns that any knowledge about the use to which fetal tissue might be put may affect a woman's decision to have an abortion, we suggest that the use of fetal material to establish EG cells is a different case. We suggest that if specific consent is required for the donation of an embryo where an immortal cell line is to be produced from it, it would be only consistent to require special consent for the production of such a cell line from fetal tissue also. Such consent would be to the possible use of fetal tissue in research on EG cells and could not specify that the primordial fetal cells be used in an individual project, such as one that might benefit the woman. It is also clear that the decision about whether or not to have an abortion would need to be taken separately and before the specific consent to the use of fetal tissue in EG cell research or therapy was granted. Nonetheless, we recognise that the possibility of specific consent runs counter to the existing framework for fetal tissue donation which requires that explicit consent for all permissible purposes should be obtained on all occasions (paragraph 30). We suggest that the question of consent for the derivation of EG cells from donated fetal tissue be considered by the CMO's Expert Group in the context of the current regulatory framework.

33 We endorse the position taken in the Polkinghorne Review that research should not be construed so narrowly as to exclude proposals for making therapeutic use of fetal tissue and propose that a similar view should be taken on the derivation of EG cells. The Review recognised that many successful therapies begin as therapeutic research, and that once the beneficial effect of a therapeutic procedure involving the use of fetal tissue has been fully established, its repeated and widespread use will inevitably result in increased demand for tissue. **We therefore recommend that any consent obtained to the use of fetal material in the establishment of EG cell lines should also cover the use of such cell lines in therapy.**

The derivation of stem cells from somatic cells

- 34 If pluripotent stem cells could be derived from a patient's somatic cells, they would have the potential to produce tissues which would allow autologous²⁴ transplant of a specific tissue type. The value of such tissues is that they would avoid the graft rejection which will accompany the use of ES cells derived from donated embryos. We recognise that research into the means of deriving pluripotent stem cells from somatic cells will, in the early stages, involve research into SCNT. It is hoped that such research will show how the nucleus of a somatic cell can be 'reprogrammed' so that a pluripotent stem cell could be derived from it. Such studies require a great deal more research. It is not yet known whether SCNT, which has the potential to produce stem cells and which has been demonstrated in some species, has the same potential in humans. Research on human embryos derived from SCNT will be essential for the safe development of the technology. Under the HFE Act, research involving embryos is legally permissible only if it is for one of the five purposes listed in paragraph 11.
- 35 The prospect of conducting research on SCNT in humans has raised a number of concerns. There is the existing moral concern outlined in paragraph 27 about creating embryos solely for the purposes of research. As we have noted, research involving the creation of new embryos is already permissible under current UK law and licences for research have already been granted (paragraphs 11 and 26). The use of SCNT would also require a source of oocytes. The HFEA has already considered the regulatory framework for the use of human oocytes in research.²⁵ It is currently permissible to use oocytes for this purpose if they have been donated with prior written consent from living or deceased donors. The availability of donated mature oocytes for infertility programmes is already limited. We are aware that immature oocytes are produced from routine surgery and that research on oocyte maturation may enable donated material of this kind to be used for SCNT. Nevertheless, this is likely to take several years. The recent reported use of cow oocytes for the culture of ES cells in the US raises the question of whether embryos created in this way would fall under the regulation of the HFE Act.²⁶ **We**

²⁴ An autologous transplant uses tissues taken from an individual, or grown from an individual's cells. When reimplanted, such cells and tissues do not provoke immune rejection.

²⁵ Human Fertilisation and Embryology Authority (1994) **Donated Ovarian Tissue in Embryo Research & Assisted Reproduction**, Human Fertilisation and Embryology Authority, London.

²⁶ The HFE Act does not discuss the use of animal oocytes in SCNT. The Act forbids combining animal gametes and human gametes but is silent on the combination of animal gametes and human somatic cells. It would be a matter for the Courts to

recommend that the HFEA seeks clarification of the regulatory status of this kind of research in the UK prior to any proposed amendment of the HFE Act.

- 36 There will inevitably be concerns about the possibility that, if research on SCNT in humans is licensed, such developments will increase the likelihood of human reproductive cloning. This is because an embryo created by SCNT may have the potential to develop normally if implanted in a uterus. Some have argued that once the technology exists to form human embryos derived through SCNT for the purpose of ES cell research, it will encourage the abuse of the technology for the purposes of human reproductive cloning even though such a procedure is not permissible under the HFE Act. However, we consider that the proposed creation of embryos using SCNT for research into the derivation of stem cells offers such significant potential medical benefits that research for such purposes should be licensed. Research on cells in culture and animals should precede and inform any experiments on human embryos derived from SCNT.
- 37 It is hoped that research into SCNT will eventually permit researchers to re-programme the nuclei of somatic cells in such a way that the resulting cells differentiate directly into stem cells thus avoiding the need for a source of oocytes and the subsequent development of an embryo. Before such developments can be realistically contemplated, a great deal more research in animal and human cells is needed to gain a better understanding of how different types of cells originate and how they are maintained. Procedures involving reprogramming of the somatic cell nucleus that did not involve embryos or oocytes would not come under HFEA regulations.
- 38 Research involving embryos derived from SCNT is legally permissible if it is for one of the purposes set out in Schedule 2 of the HFE Act (see paragraphs 11 and 34). We have recommended that Schedule 2 be amended to permit research involving embryos for the additional purpose of developing tissue therapies from the derived ES cells (see paragraph 22). If adopted, this recommendation would also permit research on embryos derived from SCNT to be licensed for the purpose proposed. We note that the proposed use of SCNT is for research into means of deriving a source of stem cells from somatic cells and that there is no intention to involve reproductive cloning, which is illegal under HFEA regulations. Moreover, we consider that it would be unacceptable for an embryo derived from SCNT to be placed in a

decide whether the embryo developing from such a hybrid cell was 'human' and thus subject to the Act.

uterus and allowed to develop to the point where it could be aborted and the organs used. The use of a fetus in this way would fail to accord it the respect owed to it as a potential human being. Such a procedure is not permissible under the HFE Act.

Implications for policy and regulation

Commercial and patent issues

- 39 Established stem cell lines can have considerable commercial value. A detailed discussion of patenting and commercial issues and the claims of donors and users of tissue is set out in the NBAC Report and our earlier report entitled **Human tissue: ethical and legal issues**, and those discussions are not reproduced here. We note that in the US, public concerns about the derivation of EG and ES cells may lead to public funding not being allocated to this area of research. Under these circumstances, US commercial organisations are likely to develop the majority of ES and EG cell lines. Such a consideration in isolation is clearly not a sound basis for arguing that the derivation of stem cells should be supported by UK public funds. If, however, the derivation and therapeutic use of stem cells are judged to be ethically acceptable and have wide-ranging potential benefits for large numbers of patients, UK public investment in the technology may be needed so that potential therapies are available at an affordable cost to the National Health Service (NHS). Patent applications have been made for the technology used by the US company Geron to derive ES and EG cell lines. We consider that the technologies to produce and make use of stem cells may have the potential to result in many therapeutic applications and, thus, should not be unduly restricted by overly broad patents. **We recommend that the granting of over-generous patents with broad claims in this important field should be discouraged.**

Regulation of stem cell lines

- 40 Research which uses stem cell lines or their products requires approval by research ethics committees (see paragraph 16). Yet, if the use of stem cells became an accepted therapeutic procedure, review by research ethics committees would no longer be required and the use of cells in therapy would be covered by normal hospital regulations. There is a divide between, on the one hand, drugs and devices which are rigorously regulated, and, on the other, procedures which are subject to relatively little regulation. While it is in the interest of those using the cell lines to ensure that they are used safely and efficiently, are additional safeguards needed? Although we have no reason to believe that stem cell therapy would raise public health concerns, **we recommend that expert**

advice be sought to evaluate the possible implications for public health.

- 41 Is there then a need for a regulatory authority to license ES and EG cell lines? What abuses would such regulation be designed to prevent? Certain forms of commercial exploitation and contractual terms concerning cell lines may be considered unacceptable. Should some possible applications of stem cell therapy, such as cosmetic rejuvenation, be banned? There may be particular forms of stem cell therapy which should be closely regulated. Consideration may also be required of how to manage the demand for forms of stem cell therapy. Would the queuing system that is currently used for transplantation recipients be an appropriate model?
- 42 In the early stages of stem cell research it would be useful to have some form of control or oversight, such as that for organ transplantation where a regulatory framework covers donation and living transplants. Proposed uses of stem cells could be considered within the Department of Health alongside other therapies. One proposal is that the HFEA's remit should be extended to cover responsibility for stem cell lines, although it has been suggested that the Authority would resist such a move. An alternative would be to consider the expansion of the remit of the Gene Therapy Advisory Committee (GTAC) to include the therapeutic non-reproductive use of stem cell lines. GTAC could consider safety issues in patients, including long-term follow-up, a role analogous to its current responsibilities concerning gene therapy.

Summary

- 43 After considering the issues related to the therapeutic use of stem cells we have reached some conclusions and have highlighted issues for further consideration. We summarise our findings below.
- The ability to culture stem cells indefinitely and to control how such cells specialise to form the different tissues of the body offers the possibility of major advances in healthcare (paragraphs 1-2).
 - We consider that the removal and cultivation of cells from a donated embryo does not indicate lack of respect for the embryo (paragraph 21). This research involves using the embryo as a means to an end but, since we accept the morality of doing so in relation to currently authorised embryo research, there seems to be no good reason to disallow research on the embryo where the aim is to develop therapies for others. **We therefore recommend that research involving human embryos be**

permitted for the purpose of developing tissue therapies from the derived ES cells and that Schedule 2 of the HFE Act be amended accordingly (paragraph 22).

- We consider that the use of embryonic tissue in research projects to establish ES cell lines raises different issues relating to consent than other forms of research permissible under Schedule 2 of the HFE Act. Consequently, where specific research regarding the establishment of an ES cell line is contemplated, embryo donors should be asked explicitly whether or not they consent to such research and subsequent therapeutic use of the cell line. We endorse the relevant recommendations of the US NBAC Report (paragraph 25).
- While there are sufficient and appropriate donated embryos from IVF treatments for use in research, we consider that there are no compelling reasons to allow additional embryos to be created merely to increase the number of embryos available for ES cell research or therapy. However, we suggest that this issue be kept under review (paragraph 27).
- We do not consider that concerns about inappropriate incentives resulting from a potential benefit deriving from the establishment of an EG cell line are so great that the donation of fetal tissue for such purposes should be prohibited. We suggest that the provisions in the Polkinghorne Review designed to separate the decision to have an abortion and the decision about any use which can be made of the fetal material are sufficient to meet such concerns. We suggest that if specific consent is required for the donation of an embryo where an immortal cell line is to be produced from it, it would be only consistent to require special consent for the production of such a cell line from fetal tissue also. We suggest that the question of consent for the derivation of EG cells from donated fetal tissue be considered by the CMO's Expert Group in the context of the current regulatory framework (paragraph 32).
- We endorse the position taken in the Polkinghorne Review that research should not be construed so narrowly as to exclude proposals for making therapeutic use of fetal tissue and propose that a similar view should be taken on the derivation of EG cells. **We therefore recommend that any consent obtained to the use of fetal material in the establishment of EG cell lines should also cover the use of such cell lines in therapy** (paragraph 33).
- The recent reported use of cow oocytes for the culture of ES cells in the US raises the question of whether blastocysts created in this way would fall under the regulation of the HFE

Act. **We recommend that the HFEA seeks clarification of the regulatory status of this kind of research in the UK prior to any proposed amendment of the HFE Act.** (paragraph 35).

- However, we consider that the proposed creation of embryos using SCNT for research into the derivation of stem cells offers such significant potential medical benefits that research for such purposes should be licensed. Research on cells in culture and animals should precede and inform any experiments on human embryos derived from SCNT (paragraph 36). Research involving embryos derived from SCNT is legally permissible if it is for one of the purposes set out in Schedule 2 of the HFE Act. We have recommended that Schedule 2 be amended to permit research involving embryos for the additional purpose of developing tissue therapies from the derived ES cells. If adopted, this recommendation would also permit research on embryos derived from SCNT to be licensed for the purpose proposed. We consider that it would be unacceptable for an embryo derived from SCNT to be placed in a uterus and allowed to develop to the point where it could be aborted and the organs used (paragraph 38).
- **We recommend that the granting of over-generous patents with broad claims in this important field should be discouraged** (paragraph 39).
- Although we have no reason to believe that stem cell therapy would raise public health concerns, **we recommend that expert advice be sought to evaluate the possible implications for public health** (paragraph 40).