



postnote

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STEM CELL RESEARCH

In January 2001, Parliament agreed regulations to allow research for therapeutic purposes on cells derived from human embryos. As part of this agreement, a House of Lords Select Committee on Stem Cell Research was formed to examine the issues in more detail. This briefing sets out recent legal and technical developments in the area of stem cell research and considers the issues they raise.

Legal Background

In 1978 the birth of Louise Brown – the world's first 'test-tube baby' – in Oldham prompted a debate on this new technology. Because in-vitro fertilisation (IVF) involved creating human embryos outside the body, the debate considered what to do with any 'spare' embryos and whether it was morally acceptable to allow research on human embryos. This led to the setting up of a UK framework for regulating research on human embryos:

- The Warnock Committee (1982-84) recommended research on human embryos should be allowed (subject to controls) up to 14 days after fertilisation.
- The Human Fertilisation and Embryology (HFE) Act 1990, which set up a statutory body (HFE Authority - HFEA) to regulate research on human embryos. It allowed embryo research up to 14 days for five specified purposes (box 2) concerned with increasing knowledge about embryo creation and development.
- Three further purposes were introduced by the HFE (Research Purposes) Regulations in January 2001, to allow research for therapeutic purposes (box 2).

A judicial review was sought by the ProLife Alliance in November 2001 to clarify the scope of the HFE Act.

Among the main features of this legal challenge were:

- What constitutes an embryo? The Act defines an embryo in terms of fertilisation ("a live human embryo where fertilisation is complete"). But new techniques (cell nuclear replacement, see box 3) can create cells that behave like embryos without using fertilisation.
- The High Court ruled that such cells were **not** regulated by the Act because their creation did not

Box 1 Stem cells

What are they? – stem cells have the capacity to renew themselves, and the potential to differentiate into different cell types. They can be isolated from:

- human embryos that are a few days old (embryonic stem or ES cells);
- aborted human foetuses;
- umbilical cord blood (placental stem cells);
- humans at all later stages of development (e.g. from bone marrow and many other types of adult tissue).

Stem cells from these sources vary in a number of respects.

Plasticity – i.e. the range of different cell types the cell can give rise to. ES cells have the potential to turn into each of the hundreds of different cell types found in the body (this is what happens naturally during embryo development). Stem cells isolated from later stages of development (e.g. most foetal cell types, placental or adult stem cells) were thought to have a more limited plasticity, because they have already differentiated to some extent. But it is now thought that cells of one type (such as neural stem cells) may be able to **dedifferentiate** into cells of another type (e.g. blood cells), although the process by which this occurs is not understood.

Isolation and culture – therapeutic use of stem cells will require large numbers to be cultured in the laboratory. ES cells are relatively easy to isolate and culture up to the cell numbers likely to be needed for therapy. Adult stem cells may be more difficult to identify and isolate as they represent a progressively smaller proportion of the cell population with age. It is also not clear how many different types of adult stem cells there are in the body; where such cells are known to exist, they may not be readily accessible.

involve fertilisation, leading to fears that the Act could not be used to prevent human reproductive cloning.

- This decision was overturned in the Appeal Court, following a government appeal in January 2002. The Court ruled that a cell created by nuclear replacement is an embryo and thus falls within the HFE Act 1990.
- In response to the original High Court ruling, the government introduced the Human Reproductive Cloning Act 2001 to ban reproductive cloning by prohibiting "the placing in a woman of a human embryo ... created otherwise than by fertilisation".

Box 2 The HFE Act 1990

The HFE Act 1990 established a statutory body – the HFEA. Together, these regulate and monitor:

- any fertility treatment involving donated eggs, sperm or embryos created outside the body;
- storage of eggs, sperm and embryos;
- research on human embryos.

All research involving the creation, storage or use of human embryos outside the body must be licensed by the HFEA. Such research can only be licensed where it is “*necessary or desirable*”, where use of human embryos is essential and, under the original terms of the Act, where it is for one of five purposes to increase knowledge about the creation and development of embryos:

- promoting advances in treatment of infertility;
- increasing knowledge on causes of congenital disease;
- increasing knowledge on causes of miscarriage;
- developing more effective techniques of contraception;
- developing methods for detecting gene/chromosome abnormalities in embryos prior to implantation.

In January 2001 the HFE (Research Purposes) Regulations were passed to allow research on embryos to be licensed for three additional (therapeutic) purposes:

- increasing knowledge about development of embryos;
- increasing knowledge about serious disease;
- enabling any such knowledge to be applied in developing treatment for serious disease.

Regenerative therapy

The potential of regenerative therapy

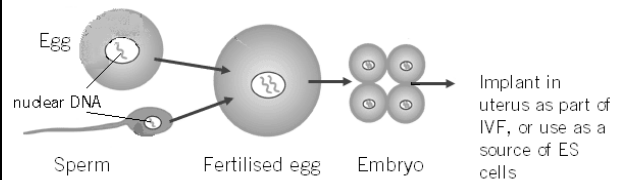
A driving force behind the amendments to the HFE Act was the prospect of using human stem cells (box 1) for therapeutic purposes (regenerative therapy). Among the most commonly cited potential applications are treatment of fractures, burns and other injuries, as well as developing effective therapies for a range of serious degenerative conditions such as Parkinson’s, Alzheimer’s, diabetes, and certain types of heart disease. Such diseases are a major cause of illness and death and, for many of them, no effective treatment currently exists. At present the most widely used stem cell-based therapy is bone marrow transplant. Future regenerative therapies could transplant tissue containing stem cells into diseased or damaged tissue. It is also likely that therapies will be developed that use stem cells purified and cultured in the laboratory. These could be administered to patients as undifferentiated cells or the stem cells could be differentiated to cells of the appropriate type in the laboratory and then used for therapy. A final possibility is transplanting tissues made in the laboratory using differentiated stem cells. While there is widespread agreement over the potential therapeutic benefits of stem cells, further research is required before such therapies become a reality.

Immune rejection and other limitations

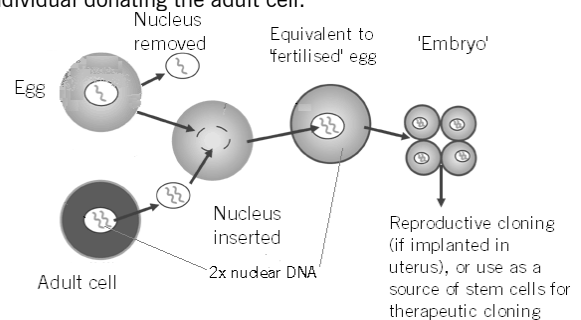
Each cell in the body carries a unique ‘signature’ that marks the cell as belonging to an individual. Transplanted organs or grafts will not carry this signature, will be regarded as ‘foreign’ and attacked by the body’s immune system, causing rejection. Strategies for minimising immune rejection include the use of drugs to suppress the immune system, and ‘matching’ donated tissue to patients. Stem cell therapies offer a number of potential ways round the problem of immune rejection.

Box 3 Fertilisation, nuclear replacement & cloning

Fertilisation – a sperm, carrying a single copy of the father’s genes fuses with an egg, which contains a single copy of the mother’s genes. The resulting fertilised egg contains a genetically unique recombination of the parent’s DNA (see diagram below).



Cell nuclear replacement – the nucleus from an adult cell is inserted into an egg from which the nucleus has been removed (see diagram below). In some circumstances, factors present in the egg **re-programme** the adult nucleus, and the cell behaves as if it were an embryo. The resulting embryonic cells contain nuclear DNA identical to that of the donor of the adult cell. Embryos created in such a way could be used for **reproductive cloning**, being implanted into a female to give rise to clones of the individual donating the adult cell; this is the procedure that created Dolly the sheep. Alternatively, they can be used for **therapeutic cloning** to create embryonic stem cells for regenerative therapy for the individual donating the adult cell.



Approaches (box 4) include the setting up of stem cell banks, developing therapies based on use of the patient’s own cells, using therapeutic cloning to produce ‘bespoke’ stem cells that will not be rejected and even genetically modifying stem cells to alter their immunological profile.

The therapeutic strategies outlined above also raise several safety concerns and other potential drawbacks:

- The need to ensure that cell lines are pure and that stem cells do not differentiate into unwanted cell types. This may be an issue of particular concern for therapies involving undifferentiated ES cells.
- Uncertainties about therapies using de-differentiated (adult) stem cells or re-programmed ES cells from therapeutic cloning (see box 3). Such manipulations may have unforeseen consequences – for instance if the cells retain some ‘memory’ of their previous (differentiated) state.
- The need to develop better culture methods. ES and adult stem cells currently have to be co-cultured with animal ‘feeder’ cells (that provide essential growth factors) which makes them unsuitable for therapy.
- The need for further research into how to control stem cells used in therapy. This was highlighted by a recent trial using foetal stem cells to treat Parkinson’s disease, where the uncontrolled release of dopamine led to some of the patients’ symptoms getting worse.

The House of Lords Stem Cell Research Committee considered these issues and recommended that the Department of Health (DH) set up a new advisory body¹ to oversee clinical trials involving stem cells.

Embryonic stem cells

Ethical considerations

Is research on human embryos justifiable?

In the mid-1980s, the Warnock Committee took evidence representing a wide spectrum of views on the status of the early embryo. At one end of the spectrum were those who believe that the human embryo should be afforded the same respect as any person from the moment of fertilisation. At the other end were those who believe that the early human embryo deserves no more respect than any other isolated human tissue.

The Warnock Committee took a view between these two positions, regarding the early human embryo as having a special status, but not one warranting the same level of protection afforded to a fully developed human. In this (gradualist) view, the degree of protection afforded varies with the stage of development. This was reflected in the HFE Act, which allowed research on human embryos (subject to other conditions) up to 14 days after fertilisation. The House of Lords Stem Cell Research Committee weighed the ethical arguments carefully in its recent report. While respecting the views of those who regard any research involving the destruction of a human embryo as wrong, it concluded that in light of the current law and social attitudes, it was *“not persuaded that all research on early human embryos should be prohibited”*.

The 14 day limit

Inherent in the gradualist approach enshrined in the HFE Act is that a transition point has to be selected beyond which the degree of protection afforded to a human embryo increases. The Warnock Committee chose a 14 day limit for research on human embryos because this is the point at which the precursor to what will eventually develop into the nervous system becomes apparent. Although this is a somewhat arbitrary limit, the Lords Stem Cell Research Committee noted that it seems to have been widely accepted in practice, and recommended that 14 days *“should remain the limit for research on early embryos”*.

Creating embryos for research

The Warnock Committee decided by a slender majority² that research on human embryos created solely for such purposes was permissible. In practice, the vast majority of embryo research carried out under the HFE Act has involved surplus embryos from IVF programmes³. The House of Lords Committee on Stem Cell Research considered this issue, deciding that it was preferable to use ‘spare’ IVF embryos for research (which would otherwise be destroyed) than to create embryos (which would have no prospect of being implanted) specifically for research. It took the view that *“embryos should not be created specifically for research purposes unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos”*.

Box 4 Minimising immune rejection

Among the main approaches available are:

- Selecting matched stem cell lines – this is an extension of the current practice of matching donated tissues to patients. It would involve setting up banks of stem cells for each of the main types of immunological signature – estimates for the number of different types needed vary between several hundred and several thousand.
- Using a patient’s own cells – it may be possible to isolate stem cells of the type needed from the patient, multiply them in the laboratory and use them for therapy. In practice this approach may be limited by the time taken to culture sufficient numbers of cells. A variation might be possible where abundant cells (e.g. blood) are taken from the patient and dedifferentiated (box 1) into cells of the type needed for therapy, although research has yet to show unequivocally that such an approach is possible.
- Therapeutic cloning (box 3) – this can be used to isolate ES cells for use in therapy. Such cells should be identical to the patient’s own cells, and thus not be rejected. However, it is not clear that the technology could be developed to be sufficiently reliable, rapid and safe to be used in this way.
- Genetic modification – although a more distant prospect, it may prove possible to genetically modify stem cells to minimise immune rejection. Recent research in mice suggests that such stem cells can be successfully transplanted into other mice.

Cell nuclear replacement (CNR)

The House of Lords Committee on Stem Cell Research also considered the use of CNR to create embryos. It noted that the main opposition to using CNR was grounded in concerns that embryos so created might be used for reproductive cloning. However, the Committee was satisfied that the current regulations (including the recent statutory prohibition) were sufficient to ensure that the development of CNR would not lead to reproductive cloning in the UK. It concluded that there was a powerful case for using CNR (subject to strict regulation by the HFEA) *“as a research tool to enable cell-based therapies to be developed”*.

Is research on ES cells necessary?

Another issue considered by the Lords Committee was whether it was necessary to use embryonic stem cells. Pro-life (and some faith) groups have argued that recent research suggesting that it may be possible to de-differentiate adult stem cells into a wide range of different cell types obviates the need for continuing research on ES cells. The Committee considered such studies to be promising, and strongly encouraged funding of further research on adult stem cells. However, it concluded *“it is unlikely that either adult stem cells or ES cells alone will provide the basis for all stem cell-based therapies; it is therefore necessary to keep both routes to therapy open to ensure maximum medical benefit”*. While it acknowledged that understanding of the processes of differentiation and de-differentiation might eventually reach a point where further research on ES cells became unnecessary, it concluded that this was unlikely to be the case for many years. In the meantime, it noted there was a strong scientific and medical case for continued research on ES cells.

Regulatory issues

The rapid pace of advance in stem cell research has led to concerns that developments are moving too fast for the regulatory process to keep up. Among the key regulatory issues considered by the Lords Stem Cell Research Committee were the adequacy of existing legislation/regulations and the possible need for further regulation to take recent developments into account.

Existing legislation/regulations

As outlined earlier, the HFE Act 1990 was recently amended by the HFE (Research Purposes) Regulations, which introduced additional purposes for which research on human embryos can be licensed. The drafting of the Regulations leaves scope for uncertainty in two main areas. Firstly, two of the additional purposes allowed by the regulations refer to 'serious disease'; this is not a term that is clearly defined in the HFE Act or in other statutes. As the House of Lords Stem Cell Research Committee has pointed out, it is not clear whether 'serious' refers to the consequences of a disease for the individual or for society, nor whether 'serious disease' encompasses serious injury (e.g. to the spinal cord). The Committee thus invited the DH and HFEA to examine the possibility of drawing up indicative guidance as to what constitutes serious disease.

Second, is the issue of whether the drafting of the new regulations actually encompasses the type of research for which licences are most likely to be sought. This arises because the new regulations refer to applied research: "*increasing knowledge*" (of the development of embryos or about serious disease) or of the "*development of treatments*" (for serious disease). However, initial research is likely to be more fundamental, targeted at understanding the basic processes of cell differentiation and de-differentiation. The Lords Committee received evidence from the HFEA that it had received legal advice that such basic research falls within the scope of the Regulations as drafted. Indeed, the Authority has already announced that it will approve licences for two UK research groups for fundamental research aimed at developing new therapies (e.g. for Parkinson's disease). But the Committee noted that "*to put the matter beyond any possible doubt, when the Government bring forward legislation they should consider making express provision for such basic research as is necessary as a precursor for the development of cell-based therapies*"

In general, the Committee felt that the existing regulatory system worked well, and that the HFEA's work was highly regarded (though not by those opposed in principle to the HFE Act). It made two main recommendations relating to the current work of the HFEA:

- The DH/HFEA should consider a review of research licensed by the HFEA to check whether the claims made for human embryo research have been realised.
- In view of the additional responsibilities placed on the HFEA by the HFE (Research Purposes) Regulations, the Government should keep the HFEA's funding under review to ensure it is adequately resourced.

Future regulatory developments

The House of Lords Stem Cell Research Committee identified a number of other issues that the regulatory system may have to address and these include the:

- Regulatory status of human cells created by cell nuclear replacement (CNR) and similar techniques. Fears that such cells might be used for human reproductive cloning have been allayed by the recent statutory prohibition of such activities. The recent Appeal Court ruling also means that cells created by CNR are currently regulated by the HFEA, although this could be the subject of further legal challenge. A number of other reprogramming techniques could potentially be used to produce human cells that can behave like embryos - as such methods do not involve fertilisation, it is unclear whether research using them would be subject to current regulations.
- Regulatory status of cells created by mixing human and animal material (e.g. nuclei from adult cells with eggs from animals). A report from the Chief Medical Officer in 2001 noted the HFE Act did not control such research. The Lords Committee suggested that (if practicable), some might see this as a more ethically acceptable way of creating human ES cells than using embryos created by CNR with human eggs.
- Developments in research on adult stem cells. As noted previously, the Lords Committee concluded that, given the current state of knowledge, research on both ES and adult stem cells was needed. However, the Committee recommended the Government undertakes a review of scientific developments in this area towards the end of the decade to determine whether research on human embryos is still necessary.
- Regulation of established stem cell lines. The Medical Research Council (MRC) has announced that it will set up a national stem cell bank governed by a steering committee. The Committee endorsed this approach, suggesting that the steering committee should also establish a code of conduct for use of ES cells covering issues such as informed consent. It recommended that HFEA should make it a condition of each licence that any ES cell line generated by research be deposited in the cell bank; HFEA should check no suitable cell lines are available in the bank before granting each licence.

Endnotes

- 1 The Committee envisaged a body along the same lines as GTAC (the Gene Therapy Advisory Committee).
- 2 Of the 16 members of the Warnock Committee, 3 felt that research on embryos should not be permitted at all; a further 4 that research should not be allowed on embryos created solely for research.
- 3 HFEA figures show that between August 1991 and March 1999, 53,497 embryos from IVF programmes were donated for research compared to the 118 embryos created for research.

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of public policy issues that have a basis in science and technology. POST would like to thank Palwinder Kaur for her assistance in the preparation of this briefing note.

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