Comparative Primordial Stem Cell Regulation: Canadian Policy Options

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Human stem cells can be derived from a number of sources and offer fertile areas of scientific research that hold great medical potential. Some stem cells are found in human umbilical cord blood,[1] some in placental tissue and recent research has focused on the medical potential of somatic or "adult" stem cells.[2] However, by far the most controversial of human stem cells are primordial stem cells, known as human embryonic stem (ES) and germ cells (EG). ES and EG cell research offers the potential of great medical benefit, in particular, the potential to provide an endless supply of transplantable tissue. The source of these cells, being human embryos and aborted foetuses respectively, raises difficult ethical issues and complicates policy development.

With respect to the policy dimensions of primordial stem cell oversight, a number of existing regulatory schemes may provide partial or adequate regulation. These include human subjects research regulation, embryo research regulation, foetal tissue research and use regulation, research funding legislation and guidelines, practice guidelines for use of human biological materials, health and safety legislation and criminal law, among others.[3]

There has been considerable interest in the use of stem cells for therapy in the international community.[4] This paper will canvass the responses, conclusions and recommendations of various governmental and non-governmental bodies to the issue of stem cell research. Particular emphasis will be placed on the responses of the United States and the United Kingdom, with reference to the response of the ethics advisory group to the European Commission and statements by Germany and the Vatican. Primary focus will be placed on the use of ES and EG cells as a source of stem cell research. Existing Canadian regulations will be examined to determine whether Canadian policy is sufficient to deal with research and use of primordial stem cells or whether new policy is needed.

Background

At the end of 1998, almost simultaneously, one team of researchers announced that it had isolated human embryonic stem (ES) cells[5] and another announced that it had isolated human embryonic germ (EG)

[1] See the European Group on Ethics in Science and New Technologies to the European Commission (EGE) Opinion No. 15 *Ethical Aspects of Human Stem Cell Research and Use*, 14 November, 2000. Hass J. 1999, "A little biological insurance." *The Globe and Mail*, 11 May, A19.
[2] 2000, "Breakthrough in stem cells set to fuel row over embryo research." *Agence France Presse*, 19 September.
[3] It is not within the scope of this paper to examine all these sources of regulation, however several Canadian regulatory structures are examined below.
[4] See L. P. Knowles, "International Perspectives on Human Embryo and Foetal Tissue Regulation" in National Bioethics Advisory Commission *Ethical Issues in Human Stem Cell Research*, Vol 2 Commissioned Papers.
[5] James A. Thomson and his colleagues at the University of Wisconsin made the announcement of the isolation of ES cells. Thomson's team isolated ES cells from "spare embryos"; that is, embryos created in a fertility clinic by IVF (in vitro fertilization) that are no longer needed for transfer to a woman.

cells.[6] Embryonic stem cells are derived from five-to-seven day old embryos known as blastocysts. If implanted, the outer layer of the blastocyst is destined to become the placenta. The remainder of the blastocyst, called the inner cell mass, is destined to become the foetus. Embryonic stem cells are isolated from this inner cell mass and the derivation of these cells necessarily involves the destruction of the embryo. Embryonic germ cells are derived from immature aborted foetuses. They are derived from a small set of stem cells that were set aside in the embryo and prevented from differentiating. They are referred to as embryonic *germ* cells because they were destined to give rise to the eggs or sperm of the next generation.[7] EG cells are not, however, the same thing as foetal eggs, they are the precursors to the cells that might eventually become foetal eggs if the foetus was female and proceeded to term.

Why are primordial stem cells relevant?

ES and EG cells have two noteworthy properties. First, the cells are thought to divide indefinitely when cultured in cell lines, which makes them excellent tools for manipulation by researchers.[8] Second, they are said to be *pluripotent*.[9] Other cells in the human body are differentiated to some degree, which means that they have turned into a specific type of cell, such as blood, nerve or skin cells. By contrast, ES and EG cells can turn into many cell types. As of yet, researchers have not been able to successfully direct their differentiation to an extent that would be clinically useful, however, the hope is that someday soon these cells will be used to generate specific, transplantable tissues.

What are the ethical issues that generate the controversy about ES and EG cell research?

Despite the potential for medical benefit offered by ES and EG cells, the origin of these cells raises policy and ethical concerns. The policy issues primarily concern the use of existing legislative and regulatory schemes to govern research using ES cells and the sources of funding for research involving human embryos and foetal tissue. The ethical concerns are primarily related to the moral status of the embryo and the aborted foetus.

How one evaluates the act of deriving ES cells depends on whether one believes the human embryo is a person, a mass of human cells, or something in between which requires special respect.[10] Science cannot answer this question for us. Currently, many western countries permit embryo research for

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[6] John Gearhart and his colleagues at Johns Hopkins University announced the isolation of EG cells. Gearhart's team isolated EG cells from immature aborted foetuses.

[7] L. P. Knowles & E. Parens, *The Science and Ethics of Embryonic Stem Cell Research*, Encyclopedia Britannica: Book of the Year, 1999.

[8] *Ibid.* Note however, that the NBAC report indicates, "ES cells are not indefinitely stable in culture. As these cells are gown, irreversible changes occur in their genetic makeup." National Bioethics Advisory Commission *Ethical Issues in Human Stem Cell Research*, Executive Summary at 5.

[9] 2000, "Everything you ever wanted to know about stem cells." *New Scientist*, 19 August, 14-15.

[10] See European Commission, European Group on Ethics in Science and New Technologies, *Opinion No 12, Ethical Aspects of Research Involving the Use of Human Embryo in the Context of the 5th Framework Programme,* 23 November 1998.

specific purposes and within certain strict limits.[11] They proceed from the view that embryos have neither the moral status of persons nor that of mere cells; because of their special connection with the human community they enjoy an intermediate position that requires that they be treated with special respect.[12]

The use of foetal tissue to isolate EG cells is less problematic than the similar use of human embryos for three reasons. First, the removal of EG cells from foetal tissue does not occasion the destruction of a live foetus. Secondly, there is no question of creating foetal tissue specifically for research. Thirdly, the use of foetal tissue to develop therapies for people unrelated to reproduction has been raised before in the context of foetal tissue transplantation, and therefore a number of laws and policies exist regarding this use. Consequently, EG cell researchers and funders should be aware of safeguards and guidelines regarding the use of foetal tissue in research.[13]

International policy recommendations for ES and EG cells research

The United States

EG cell research:

Human foetal tissue has been used in research aimed at developing therapies for disorders, such as Parkinson's disease, by transplanting that tissue into afflicted people. Prior to 1993, laws in the United States prohibited the use of federal funds for this research since the tissue used is obtained from aborted foetuses. In 1993 President Clinton lifted that ban. A number of restrictions exist to ensure that foetal tissue for research is obtained in a manner that respects the women from whom it is taken, and that such research does not encourage abortion.[14] These restrictions can and should apply to EG cell research.

Limitations of the use of foetal tissue in transplantation include three main restrictions. First, the physician is required to obtain the woman's informed consent to use foetal tissue removed from her body. Second, to ensure that the possibility of donating tissue to benefit medical science does not influence a

[11] L.P. Knowles, "Primordial Stem Cell Regulation: Implications of Assisted Reproductive Technology Policies Among Nations" Journal *of Women's Health and Law* 1999, p.19-51. See *infra* information on the United States and the United Kingdom.

[12] See *Proceed with Care: The Final Report of the Royal Commission on New Reproductive Technologies,* Vol. 1, Minister of Government Services Canada, 1993, p. 632. (*Proceed with Care*).

[13] In the United States see *DHHS Regulations for the Protections of Human Subjects*, 45 CFR 46 §46.210, and *NIH Reauthorization Act* (1993) Ss. 111, 112 amending *Public Health Service Act*, 42 USC 289 et seq. For international regulations see for example: United Kingdom, Committee to Review the Guidance on the Research Uses of Foetuses and Foetal Material. *Report* (The Polkinghorne Report) London: HMSO, 1989 [hereinafter *Polkinghorne Report*]; World Medical Association, *Foetal Tissue Transplantation Statement*, 1989, Canada, *Tri-Council Policy Statement*, at 9.4 and *Proceed with Care,* Vol 2 at 967-1015; Australia, National Health and Medical Research Council *Statement on Human Experimentation and Supplementary Notes, 1992, Supplementary Note 5 - The Human Foetus and the Use of Human Foetal Material*; France, *Opinion No. 53*.

[14] *DHHS Regulations for the Protections of Human Subjects*, 45 CFR 46 §46.210, and *NIH Reauthorization Act* (1993) Ss. 111, 112 amending *Public Health Service Act*, 42 USC 289 et seq.

woman's decision, the donation of foetal tissue can only be discussed following a decision to terminate the pregnancy. Finally, restrictions mandate that a woman cannot direct that her foetal tissue be used to benefit a particular person. Both the National Bioethics Advisory Commission and the National Institutes of Health indicated that these guidelines should be expanded to apply to EG cell research.[15] Changes to the informed consent required to use foetal tissue would mirror those indicated below with respect to the use of donated embryos, including specific consent to the use of the tissue for stem cell research.[16]

ES cell research:

In the United States, existing federal law prohibits federal funding of research using human embryos.[17] The law limits the ability to conduct research on embryos that would lead to the discard or destruction of the embryo, in which case only interventions intended to benefit the embryo and conducted on embryos intended for implantation would be permissible. Consequently, private corporations have taken the lead in this research and have, as mentioned above, isolated the first human ES cells. In November 1998 President Clinton appealed for guidance to the National Bioethics Advisory Commission (NBAC).[18] In January 1999 the Director of the National Institutes of Health (NIH) issued a moratorium on NIH-funded research using human pluripotent stem cells derived from human embryos and foetal tissue pending examination of the law. That same month the NIH received a legal opinion that the current law can be interpreted so that it is legal to fund research on human ES cells so long as federal funds are not used to support the *derivation* of those cells.[19]

Although this legal interpretation may be technically sound, it places the American government in the paradoxical position of withholding funds from research to derive ES cells but permitting funds for research on ES cells once they have been derived using private funds, or once they have been imported from countries without restrictions on embryo research. This paradox is explicitly acknowledged by the French National Commission: "We are approaching a paradoxical situation as a result of legislation: … experimentation or therapeutic research on [stem cells] from embryos *in vitro* are banned, but it is possible to import cells from collections established without any observance of specific ethical law applicable in France to embryonic cells".[20] The same situation applies in Australia where research on ES cells is being

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[15] National Bioethics Advisory Commission *Ethical Issues in Human Stem Cell Research*, Executive Summary at 4, NIH Guidelines, Part IIB.
[16] See *infra*.
[17] *Departments of Labor, Health and Human Services, and Education, and Related Agencies in the Omnibus Consolidated and Emergency Supplemental Appropriations Act,* Fiscal Year 1999, Public Law 105-277, S.511.
[18] This appeal was spurred in part by news that bovine eggs had been fused with human DNA to create embryos as a source for stem cells. Wade, N. 1998, "Researchers Claim Embryonic Cell Mix of Human and Cow." *New York Times* 12 November, A-1.
[19] 1999 "Embryonic stem-cell research exempt from ban, NIH is told." 397 *Nature*, 21 January, 185.
[20] French National Consultative Ethics Committee for Health and Life Sciences, *Opinion No. 53,* "Opinion on the establishment of collections of human embryo cells and their use for therapeutic or scientific purposes," 11 March 1997. The French Conseil d'Etat recommended that the French bioethics legislation

conducted on cell lines created in Singapore.[21] Despite the foregoing, the NIH guidelines, discussed below, are based on that legal opinion.

National Bioethics Advisory Commission

In response to the President's letter of November 1998, NBAC was charged with the task of analyzing the ethical implications of primordial stem cell research and recommending directions for future regulation of this research. NBAC published its report *Ethical Issues in Human Stem Cell Research* in September 1999.With respect to EG cells, NBAC endorsed the use of foetal tissue for the derivation and use of these cells provided the restrictions in the foetal tissue transplantation laws already in effect were followed. NBAC also specifically recommended that changes are needed to make it explicit that the restrictions on the use of tissue from aborted foetuses for transplantation should apply to the research on EG cells from that tissue.[22]

NBAC debated the ethics of ES and EG research and, convinced that the promise of primordial stem cell research was great, recommended a partial lifting of the embryo research law so that embryo research, both deriving stem cells and using derived stem cells, could be eligible for federal funding.[23] Of particular importance was the finding that a distinction between the derivation of ES cells and the use of those cells was not morally relevant.[24] In addition, NBAC stated that relying on cell lines derived exclusively by privately-funded researchers could severely limit scientific and clinical progress, and would diminish the scientific value of the activities receiving federal support. NBAC gave the following reasons in support of their assertion:

- Researchers using ES cell lines will derive substantial scientific benefits from a detailed understanding of the process of ES cell derivation
- Significant basic research needs to be conducted regarding the process of ES cell derivation before cell-based therapies can be realized, and this work must be pursued in a wide variety of settings including those exclusively devoted to basic academic research
- ES cells are not indefinitely stable in culture, therefore it is especially important in the first few years of ES cell research to be able to repeatedly derive ES cells in order to ensure that the properties of the cells that are being studied have not changed.

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be amended to allow stem cell research under strict conditions and only on surplus embryos left over from IVF. It proposes the creation of a body, akin to the Human Fertilisation and Embryology Authority in the United Kingdom that would approve research protocols on a case-by-case basis.

[21] 2000, "Multi-centre team grows human nerve cells from stem cells" 355:9212 *The Lancet*, April 15, 1344.

[22] See discussion above.

[23] See National Bioethics Advisory Commission, *Ethical Issues in Stem Cell Research,* Vol. 1: Report and Recommendations of the National Bioethics Advisory Commission, September 1999.

[24] *Ibid*. Chapter 4 at 58-59. In fact, at NBAC meetings Commissioner Capron described enshrining the distinction as "disingenuous."

Consequently, NBAC recommended that provisions be enacted applicable to funding by all federal agencies that would carve out a narrow exception for funding of research to use or to derive human ES cells from embryos that are being discarded by infertility treatment programmes.[25]

In reaching this conclusion NBAC recommended the following limitations to ES cell research:

- Funding should be available only for research on embryos that were created by *in vitro fertilization* (IVF) for fertility treatments and are no longer needed by the individuals undergoing treatment
- No embryos are to be created specifically for research purposes
- Funds should not be available for the use of ES cells produced by the cloning technique Somatic Cell Nuclear Transfer (SCNT)
- Embryos and cadaveric foetal tissue should not be bought or sold
- All stem cell research should be subject to both national as well as local oversight:
  - A National Stem Cell Oversight and Review Board (SCORB) should be established to review all protocols deriving and using ES or EG cells to ensure that derivation or use is conducted in conformance with the ethical principles and recommendations contained in the report. SCORB should:
    - Be multidisciplinary in composition
    - Certify that ES and EG cell lines result from approved protocols,
    - Maintain a public registry of approved cell lines
    - Establish a database of certified and approved cell lines
    - Use the database to track the use of the cell lines and the ultimate results of the protocols to aid in policy assessment and formulation
    - Establish requirements for and provide guidance to sponsoring agencies on the social and ethical issues that should be considered in the review of research protocols that derive or use ES or EG cells
    - Provide yearly reports to the DHHS Secretary on this follow up and other relevant ethical and social issues.
  - Local review should involve protocol review of derivation protocols by Institutional Review Boards (IRBs) [26]

In addition, the Commission stated that voluntary compliance with the recommendations by the private sector should be encouraged.

[25] *Ibid.* at 70.
[26] The U.S. equivalent of Canadian Research Ethics Boards.

National Institutes of Health

The NIH published draft guidelines on the use of human pluripotent stem cells on December 2, 1999. NIH received over 50,000 comments from various groups, members of congress and private citizens in the 90-day public comment period. On August 25, 2000 the NIH published and brought into effect *National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells* (NIH Guidelines). These Guidelines lifted the January 1999 moratorium on research using human pluripotent stem cells. The NIH Guidelines apply to human pluripotent stem cells derived from foetal tissue or from embryos that are the result of IVF, are in excess of clinical need, and have not reached the stage at which the mesoderm is formed. They do not impose requirements on federal funding of research involving stem cells from human adults, umbilical cords, or placentas.

The NIH Guidelines endorsing ES and EG cell research are based on the conclusion that no single source of stem cells may be best or even suitable for all therapies. The Guidelines further highlight the importance of research comparing the potential of adult stem cells with primordial stem cells derived from embryos and foetuses in order to determine the best source for the specialized cells and tissues needed for new treatments. In addition, the Guidelines note that adult stem cells may be more limited in potential and in availability than primordial stem cells, and may be more prone to genetic defects.[27]

The Guidelines state that funds may be used to derive human pluripotent stem cells from human *foetal* tissue, but may *not* be used to derive human primordial stem cells from human *embryos*. Unlike the NBAC recommendations, the NIH Guidelines draw a distinction between the derivation and the use of ES cells; the former is not eligible for funding while the latter is. With respect to ES cells the Guidelines are similar to NBAC's recommendations in that NIH funds may be used for research on stem cells only if they were derived from embryos left over from infertility treatment. NIH-funded researchers may not use ES cells derived from embryos created by SCNT nor embryos created specifically for research by any means. The result of these Guidelines is that derivation of ES cells will be funded with private money.

The Guidelines distinguish between materials required to apply for NIH funding, conditions required for funding eligibility and research that is not eligible for NIH funding. Required in application for funds are assurances that EG cells were derived following the conditions and restrictions set out in the Foetal Tissue Transplantation laws.[28] With respect to ES cells, required in application for funds are assurances that ES cells were derived from human embryos in accordance with certain conditions and that the institution will maintain documentation in support of those assurances. Researchers seeking funding must provide the NIH not only with the research protocol proposing to use primordial stem cells but also documentation of IRB approval of the stem cell derivation protocol.

[27] See also Smaglik, P. 2000, "Embryo stem-cell work gets NIH go-ahead." 406 *Nature*, 31 August, 925.
[28] See above.

The following conditions must be fulfilled for ES funding eligibility:

- Only embryos created for purposes of fertility treatment and remaining in excess of the clinical need of the individuals seeking fertility treatment may be used in research
- No inducements, monetary or otherwise, can be offered for the donation of human embryos for research purposes
    - Fertility clinics and labs should have specific written policies and practices to ensure no such inducements are made
- There must be a clear separation between the decision to create embryos for fertility treatment and the decision to donate human embryos for stem cell research
    - To allow adequate time between decisions only frozen human embryos should be used for stem cell research
- The decision to donate embryos for stem cell research must be free from influence of researchers

- The attending physician responsible for the fertility treatment and the researcher/investigator deriving and/or proposing to utilize human pluripotent stem cells should not be the same person
    - Fertility patients are to be approached about a donation decision only when they are deciding about the disposition of excess embryos
    - No directed donation of embryonic tissue or stem cells derived from that tissue is permitted by the donors[29]
    - IRB approval is required with respect to the research protocols for the derivation of both ES and EG cells

With respect to achieving the informed consent of the embryonic tissue donors the following conditions must be satisfied:

- Researchers must specify to the tissue donor whether information that could reveal his or her identity will be retained
- Donors must be informed of possible commercial benefit resulting from research on donated stem cells and that the donor will not have access to that commercial benefit[30]
- Donors must be informed that no medical benefit will be accruing to the donor

The following types of primordial stem cell research are ineligible for NIH funding:

- Derivation of stem cells from human embryos
- Research in which stem cells are utilized to create or contribute to a human embryo

[29] This restriction would clearly have to be revisited should autologous transfer become possible.
[30] Note that an alternative that was not adopted was to deny access to commercial benefit not only to the tissue donors, but also to the researchers involved in the informed consent process.

- Utilizing stem cells derived from human embryos created for research purposes rather than for fertility treatment
- Research in which stem cells are derived using SCNT
- Research *using* stem cells derived from SCNT
- Research in which human stem cells are combined with an animal embryo
- Research in which stem cells are used in combination with SCNT for the purposes of reproductive cloning of a human.

With respect to the oversight of primordial stem cell research, the NIH Guidelines echo the recommendation in NBAC's report by providing for the creation of the NIH Human Pluripotent Stem Cell Review Group. This working group would review documentation of compliance with the guidelines for funding requests and provide a yearly report on research funded and protocols submitted.

It is important to note that the question of funding for ES cells is far from settled. The selection of the President will likely have a profound impact on the Guidelines. Given his stance on abortion, Governor Bush is unlikely to be in favour of government funding for embryo research, whereas Vice-President Gore has indicated he is supportive of ES cell research.[31] In addition, there are a number of bills currently before Congress and the Senate both expanding and restricting the use of government funding of ES cell research.[32]

The United Kingdom[33]

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 foetus or adult cells. However, the United Kingdom has one of the most respected and comprehensive models of ART regulation. Within that framework it is possible to accommodate scientific developments and adapt the legislation with minimal disruption of the system. This is discussed below in the context of ES cell research.

EG cell research:

A Code of Practice laid down by the Polkinghorne Committee in 1989 governs the use of foetal tissue, while guidance from professional and research bodies and from the Department of Health governs research more generally. The code laid down in the Polkinghorne Report is similar in its restrictions on the

[31] 2000 "Awkward inconsistencies of a stem-cell rule." 406 *Nature,* 31 August, 921.
[32] See Healy, P. 2000 "When it comes to research funds, Arlen Specter won't take no for an answer." *Chronicle of Higher Education* 12 May.
[33] In addition to the reports mentioned below the Royal Society also drafted an opinion entitled *Therapeutic Cloning: A submission by the Royal Society to the Chief Medical Officer's Expert Group,* Report of the Royal Society, (www.royalsoc.ac.uk/policy/)

use of foetal tissue to that of the United States mentioned above. These restrictions should apply to EG cell research in the United Kingdom.

ES cell research:

The *Warnock Report* issued in 1984 canvassed the ethical and policy issues with respect to assisted reproductive technologies and recommended regulatory authority and guidelines with respect to embryo research.[34] In 1990 the *Human Fertilisation and Embryology Act 1990* (HFEA) was passed. In addition to setting out limits and prohibitions on embryo research, the HFEA created a regulatory authority, the Human Fertilisation and Embryology Authority (HFE Authority), endowed with exclusive power to grant licenses necessary to conduct embryo research in the UK. Only purposes specified under the Act are eligible for licensing.

The HFEA, arguably one of the most liberal embryo research acts, makes no explicit provision for research such as stem cell research aimed at replacement of diseased or damaged tissues. However the HFEA provided a mechanism to add research purposes not currently available for licensing through amendment of the regulations to the Act. In light of the announcement of the discovery of primordial stem cells, the Human Genetics Advisory Commission and the HFE Authority (HGAC/HFEA Statement) issued a joint report including the following statement in December 1998:

> [W]hen the 1990 HFE Act was passed, the beneficial therapeutic consequences that could potentially result from human embryo research were not envisaged. We therefore recommend that the Secretary of State should consider specifying in regulations two further purposes to be added to the list [of approved purposes], being:
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> - Developing methods of therapy for mitochondrial diseases
> - Developing methods of therapy for diseased or damaged tissues or organs.[35]

In addition, the HGAC/HFEA Statement specifically recommended permitting research of this sort, advising that it would be unwise to rule out research using cloning techniques (called Cell Nucleus Replacement [CNR] in the United Kingdom) involving embryos "that might prove of therapeutic value."[36]

The Nuffield Council on Bioethics endorsed this recommendation by the HFEA/HGAC.[37] Rather than adopting the HGAC/HFEA recommendations however, the British government responded to the report by setting up an expert advisory group to further study the need for, benefits and risks of therapeutic

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[34] *Report of the Committee of Inquiry into Human Fertilisation and Embryology,* London: HMSO, 1984 (The *Warnock Report*)
[35] *HGAC/HFEA Statement* at para. 9.3.
[36] *HGAC/HFEA Statement* at para. 5.4. The European Society for Human Reproduction and Embryology (the ESHRE) has issued a similar endorsement for the use of therapeutic cloning. See "European embryology experts offer to advise on ethics of cloning" *Nature* Vol 400 8 July 1999 at 103.
[37] *Stem Cell Therapy: the ethical issues* (www.nuffield.org.uk/bioethics/) (see *Nature* 404, 697; 2000).

cloning in humans.[38] That panel, headed by chief medical officer Liam Donaldson, issued a report to the government in May 2000 which was published August 16, 2000 entitled *Stem Cell Research: Medical Progress with Responsibility.* Among its primarily recommendations was the modification of the HFEA to permit stem cell research for the aims outlined by the HFEA/HGAC Statement above.

The following conclusions were established in the report and provide the basis for the Expert Groups' recommendations:

- The great potential to relieve suffering and treat disease provides justification for research across the range of possible sources of stem cells, including embryos
- The proposed new research uses to develop treatments for diseased tissues and organs do not raise fundamentally different ethical issues from the research uses currently permitted under the HFEA with respect to surplus embryos created by IVF for fertility treatments
- "Transitional" research on embryos created by CNR is justified by the potential benefit of understanding mechanisms for reprogramming adult cells, thereby providing compatible tissue for treatment
- A system of regulatory controls adequate to provide necessary safeguards against the inappropriate use of embryos in research exists through HFE Authority consideration of applications for research licenses
- No mechanism exists for monitoring subsequent research involving cultures of stem cells once they have been extracted from embryos

The Expert Panel made the following recommendations based on the above conclusions:

- Research using embryos, (whether created by IVF or CNR) to increase understanding about human disease and disorders and their cell-based treatment should be permitted, subject to the controls of the HFEA
- In licensing any research using embryos created by CNR, the HFE Authority must be satisfied that there is no other means to meet the needs of the research
- Donors of gametes used to create embryos for the derivation of stem cells must give specific consent to the use of their embryos to derive stem cells
- An appropriate body to establish whether the research is delivering the anticipated benefits and to identify concerns which may arise should monitor the progress of research involving ES cells.
- Mixing human somatic cells with live eggs of any animal species should not be permitted
- Reproductive cloning should remain a criminal offence

[38] 1999 "Expert group to look at UK cloning law…" 400 *Nature*, 1 July, 4. The mandate of the panel was to assess the anticipated benefits of new areas of research using human embryos, the risks and the

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

At the same time as it released the Expert Group's report, the British Government published a response to the report endorsing all of its recommendations.[39] The government subsequently drafted legislation implementing the recommendations and placed this legislation before the British Parliament for a free vote. The proposed expansion of ES cell research was passed by a vote of 366 to 174 on December 19, 2000.[40] The British government has also promised new legislation explicitly outlawing the reproductive cloning of human beings – a procedure currently prohibited under the regulations, but thought to require additional explicit condemnation. In response to the UK report and government response the Vatican condemned the proposed changes.[41] The Vatican position articulates an unambiguous condemnation of ES cell research as well as EG research which cannot be morally condoned because by using tissue from aborted foetuses it requires complicity in abortion, a practice condemned by the Catholic Church.

The Vatican

The Pontifical Academy for Life published from Vatican City, August 25, 2000 a *Declaration on the Production and the Scientific and Therapeutic Use of Human Embryonic Stem Cells.* That declaration concluded that ES cell research was in some respects not necessary given the potential for reprogramming of adult stem cells. Nevertheless, the declaration states that even if it ES cell research could be shown to be necessary, it is unethical on its own terms based on the understanding that from conception a "human identity is created, which from that point begins its own coordinated, continuous and gradual development such that at no later stage can it be considered as a simple mass of cells." Given this premise the following reasons were given to explain why ES cell research is illicit and immoral:

1. A human individual with a right to its own life is created at conception.

Consequently, any intervention that is not in favour of the embryo is an act that violates that right and is gravely immoral and illicit. The ends of ES cell research, although believed to be good, can neither justify such an immoral intervention nor make right an action that in itself is wrong.

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alternatives and, in the light of that assessment, to advise whether these new areas of research should be permitted.

[39]Government Response to the Recommendations Made in the Chief Medical Officer's Expert Group Report: "Stem Cell Research: Medical Progress with Responsibility" *Cloning* Vol 2 No 2 2000

[40] 2000 "U.K. Stem Cell Research Expansion Gets House of Commons Go Ahead." *The Blue Sheet* December 20, 15.

[41]2000 "UK posed to pass legislation to become first country in world to permit some form of human cloning." 10:16 *Transplant News*, August 28.

2. Every type of therapeutic cloning, which implies producing human embryos and then destroying them in order to obtain stem cells, is illicit.

3. ES Cells and the differentiated cells obtained from them, which are supplied by other researchers or are commercially obtainable cannot be morally used, as such a use would be morally complicit with the immoral actions of deriving those cells.[42]

A similar conclusion was drawn in Germany with respect to the ability to conduct ES cell research, but for very different reasons than those articulated by the Vatican.

Germany

The German *Embryo Protection Act, 1991* is one of Europe's strictest embryo research laws and ostensibly protects human embryos from all harmful research. In discussing the use of ES cells, the German government came to the conclusion that there was no need to relax the strict embryo protection laws to permit ES research, since EG cell research is permitted under laws relating to the use of foetal tissue.[43] Since that time, discussions have continued between those in favour of liberalising the embryo research laws to permit some ES cell research and those against all embryo research.[44] These discussions have continued in earnest since the UK recommendations were announced.[45] To date no legislation has been drafted or tabled.

The European Group on Ethics in Science and New Technologies to the European Commission (EGE)

On November 14, 2000 the EGE published Opinion No. 15 entitled *Ethical Aspects of Human Stem Cell Research and Use*. EU directives currently exist which prohibit the patenting of embryos or commercial uses of human embryos. The EGE will issue a future opinion on the ethical aspects related to the patenting of inventions involving human stem cells, consequently Opinion 15 does not address these issues with respect to stem cells.

EG cells:

With respect to EG cells, the EGE Opinion reaffirms the need to ensure that decisions to terminate pregnancy are not influenced by the therapeutic possibilities the use of fetal tissue may occasion. As with

[42] Note that this argument with respect to the complicity of one action with another is analogous to the position of the Catholic Church with respect to the use of medicines or vaccines derived from the use of aborted foetal tissue. In that case the use of the products of the research is tainted by the abortion and would render the use complicity in the abortion, considered by the Church to be illicit and immoral.
[43] DFG *Statement concerning the question of human embryonic stem cells*, March 1999.
[44] 2000 "German researchers seek legal backing for stem cell work." 404(6777) *Nature*, Mar 30, 424; 2000 "Germany edges toward stem-cell accord." 405(6786) *Nature* Jun 1, 499.
[45] 2000 "UK posed to pass legislation to become first country in world to permit some form of human cloning." 16:10 *Transplant News*, August 28.

other regions, the need for specific consent to use foetal tissue in research is required and commercial trade in this tissue is forbidden.

ES cells:

The EGE recognizes that the most promising therapeutic application of ES cells would be the production of specific cell lines for therapeutic transplantation, while recognizing that the use of these cells in clinical application is still well in the future. The EGE underscores the pluralism of the European Union (EU) by briefly outlining the different approaches to embryo research in the EU member states. Some states have embryo research legislation, some do not and some have judicial pronouncements that direct the permissible scope of embryo research. Although at a national level stem cell research is not regulated as such, that situation is in flux as several countries; notably the UK, the Netherlands and Belgium are in the process of drafting legislation.[46]

Where embryo research is permitted for research into infertility, restrictions ensure that embryos used in such research must be destroyed (i.e. cannot be implanted). Consequently, the EGE could find no argument that would prohibit the expansion of permissible embryo research to include research aimed at developing new treatments to cure severe diseases or injuries. The EGE was of the opinion that funding for this research should be available through the EU Framework programme of research, if the research complies with the ethical and legal requirements defined therein.

Specific funding should be allotted in the EC research programme for stem cell research based on spare embryos, foetal tissue and adult stem cells. The creation of embryos for stem cell production, however, was considered ethically unacceptable when spare embryos exist as an alternative source. In addition, although the EGE noted that the creation of embryos by SCNT might be the most effective way to derive stem cells that are histocompatible, they were not persuaded of the necessity to fund this research at this time. Balancing the low levels of success in SCNT and the resulting remote therapeutic prospects against considerations of trivializing the use of embryos and exerting pressure on women as a source of oocytes (the provision of cell lines would require large numbers of oocytes), the EGE concluded that the creation of embryos by SCNT for research on stem cell therapy would be premature given existing alternative sources.

Other recommendations of interest include provisions to ensure the safety of women involved in infertility treatments and the need to ensure that demand for spare embryos and oocytes do not increase

[46] The Netherlands bill which has been submitted to the Lower House for consideration is described in a brief by the Ministry of Health, Welfare and Sport, *Embryos Bill: Conditions and limitations governing the use of oocytes, spermatozoa and embryos*. That bill proposes that ES cells be cultured from spare IVF embryos only and be used only for medical research, education and other medicinal purposes. The bill

clinical pressure on these women. The EGE also underlined the need for confidentiality, free and informed consent, including specific consent to ES cell research by gamete and embryo donors, and the need to take a precautionary approach to protect the health of persons involved in clinical trials involving stem cells. Finally, the EGE emphasized that in the countries where it is permitted, it is crucial to place ES cell research under strict public control by a centralized authority, patterned along the lines of the UK HFE Authority. Authorizations to conduct ES cell research, whether carried out by the pubic or private sector, should be awarded on a highly selective basis and based on a case-by-case approach. National or European level licensing of stem cell imports and exports would be appropriate.

The foregoing description of international policy initiatives with respect to ES and EG cell research is useful in recognizing what issues connected to primordial stem cell research merited separate regulatory consideration, rather than using existing policy. The question posed is whether there exists in Canada a regulatory infrastructure that can deal with primordial stem cell research in a manner sufficient to handle the ethical and policy issues specific to these cells.

What policies exist in Canada that would apply to primordial stem cell research?

In the absence of comprehensive ART regulation in Canada, there are a few quasi-legal sources of regulatory guidance that should be examined. In 1989 the Prime Minister appointed the Royal Commission on New Reproductive Technologies (Royal Commission) to examine the social, legal and ethical implications of developments in reproductive technology. Meetings and public consultation were held over a period of two years and the commission issued its final report, *Proceed with Care: The Final Report of the Royal Commission on New Reproductive Technologies* in November 1993. Significant guidance exists in the Royal Commission's report to aid in the development of ART policy, including stem cell research, although the report has no legal force.

Drawing on the recommendations of the Commission, the Minister of Health issued a voluntary moratorium on nine reproductive technology practices in July 1995.[47] Of interest in the context of this paper were the inclusion of human embryo cloning and the creation of animal human hybrids. That moratorium continues to be in force, however, its voluntary nature means that the moratorium has no legal force *per se* including no means for sanctioning those not in compliance. Researchers receiving federal funding would likely be under pressure to conform to the health minister's call for a moratorium in order to be seen to be practicing on the highest ethical ground. To the extent that researchers choose not to comply with the voluntary moratorium they may be accused of breaching the highest articulated standards for reproductive research; consequently, the moratorium may have some persuasive or moral authority in the

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proposes a three-year ban on the creation of embryos for research purposes with provision that the ban may be reconsidered and repealed.

[47] Connor, S. 1995 "Marleau right to be cautious on reproductive technologies." *The Toronto Star,* 4 August, A25.

private as well as public research spheres. Given the lack of enforcement and sanctioning mechanisms, it is not surprising however, that there have been suggestions that the voluntary moratorium is not working.[48]

Bill C-47, a federal law, was drafted in which the recommendations of the Royal Commission were partially incorporated, including the ban of 13 reproductive technology practices. The proposed *Human Reproductive and Genetic Technologies Act,* included a ban on creating embryos for research, contrary to the recommendation of the Royal Commission. It also did not seek to establish a national regulatory and licensing body as recommended by the Royal Commission. The Bill died on Order Paper in April 1997. No further legislation has been tabled as of the writing of this paper.

In 1994 the three research councils responsible for funding research in the medical, natural and social sciences began work on a joint policy on human experimentation. The Medical Research Council (MRC),[49] National Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC) formed a working group that issued three working papers for public and academic discussion in 1994, 1996 and 1997. The Councils issued the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* in September 1998.[50] The *Tri-Council Statement* is mandatory only for those individuals and institutions applying for or receiving funding from any of the government councils. When the controversy of the independence of researchers at the Hospital for Sick Children in Toronto erupted, the MRC indicated that it would try and expand the policy statement to all research involving humans regardless of funding source.[51] To date this expansion has not been effected. While this expansion may not be possible under the current articulation of the *Tri-Council Statement*, it is important to note that there is clearly some desire to ensure that all researchers are explicitly bound by the standards articulated therein. Like the voluntary moratorium, the *Tri-Council Statement* is not binding on and therefore, has no legal force *per se* on privately funded researchers. It may, however, have persuasive or moral force in that it articulates accepted standards for ethical practice. Nonetheless, in the absence of a uniformly enforceable standard of conduct for both private and public researchers, the legal situation in Canada is somewhat similar to that in the United States: existing standards relate to public funding guidelines and the private sector acts without significant regulation or voluntarily conforms to the public funding guidelines and moratorium.

The following articles in the *Tri-Council Statement* would apply to ES cell research:

- Embryos may not be created for research purposes (Art. 9.4)

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[48] Ford, T. 1998 "There may be some good things about cloning humans." *The Toronto Star,* 30 July.
[49] The Canadian Institutes of Health Research, formally launched on June 7, 2000, replaced the MRC. See www.cihr.ca/news/press
[50] *Tri-Council Statement.*
[51] Weber J. 1998 "The Doctor vs. the Drugmaker" *Business Week* 30 November 87-88; Talaga T. 1999 "Olivieri case sparks research rules" *The Toronto Star* 28 January A8; Spurgeon D. 1998 "Canadian whistleblower row prompts broader code of conduct." 396 *Nature* 24/31 December, 715.

This article would seem to limit the ability of Canadian researchers to investigate the mechanisms of ES cell formation and cell differentiation, as the only source of embryos for research would be surplus embryos from IVF donation. It does not, however, inhibit the derivation of stem cells from embryos.

- Surplus embryos created for fertility treatments may be used in research if the gamete donors give free and informed consent to the use of the embryos in research (Art. 9.4)
- Research involving human embryos must take place during the first 14 days after their formation (Art. 9.4(d))
- Mixing of human gametes and other animal gametes is not permitted (Art. 9.3)
- REB review is required for research involving human tissue, human embryos or foetuses. (Art. 1.1(b))

The following articles are ambiguous with respect to primordial stem cell research:

- Research is acceptable only if it does not involve the genetic alteration of human gametes or embryos (Art. 9.4(b))

This article would seem on its face to result in the denial of funding for ES cell research involving SCNT that might eventually lead to autologous transfer of tissues.

- It is not ethically acceptable to undertake research that involves cloning human beings by any means including somatic cell nuclear transfer (Art. 9.5)

It is unclear whether the wording of this article would, on its own, restrict the creation of embryos by SCNT for therapeutic research.

Additionally, articles 9.1, 9.4 and 10.2 provide information on the informed consent process when using human gametes, embryos and other tissues. The information that must be communicated to prospective tissue donors includes the purposes of the research, any identifiers that might link the donor to the tissue used in research, potential commercial uses of the tissue, and implications for donor privacy.

EG cell research

Policies that address the use of foetal tissue for therapy indicate consensus exists that the guiding principles in this regulation should be respect for the woman's dignity and integrity, and respect for human life. The limitations on research involving foetal tissue in the *Tri-Council Statement* include the same limitations articulated above in the United States regulation[52] including the need to obtain free and informed consent to use the tissue, the need not to interfere with the woman's decision to continue or terminate her pregnancy, the prohibition against directed donation, and REB approval.[53]

[52] See above.
[53] Arts. 9.4 C and 10.1.

In addition, the Royal Commission advocated the establishment of a regulatory and licensing scheme to ensure that research projects using foetal tissue meet applicable ethical and scientific research standards.[54] Finally, the Commission also stated that regulations be enacted to avoid the commercialization of foetal tissue. The Canadian Royal Commission states that the non-commercialisation of reproduction is one of their guiding principles. They recommended that no for-profit trade be permitted in foetal tissue and recommend that the "prohibition on commercial exchange of foetuses and foetal tissue extend to tissues imported from other countries."[55] Whether similar restrictions should apply to ES and EG cell lines is unclear.[56]

How might Canadian Policy address Primordial Stem Cell Research?

The Canadian government has three broad choices for policy development with respect to primordial stem cell research:

1. *Stay with the status quo*

One option open to the Canadian government is to make no changes to the current regulatory structure. This option would leave the voluntary moratorium and the *Tri-Council Statement* as the primary regulatory guidelines within which stem cell research would be addressed. It is the opinion of this author that, as currently drafted, this regulatory structure is not sufficient to deal with the advent of stem cell research. The conclusions of the Expert Panel from the United Kingdom articulate why stem cell research needs to be specifically addressed in regulation.[57] In addition, there is little question that currently unanticipated uses of stem cells will be developed in the future; leaving the current framework in place to deal with future scientific developments in this field could impede socially beneficial scientific research and will likely create or exacerbate division between public and private funding in Canadian embryo research for several reasons:

- There are ambiguities in the *Tri-Council Statement* when applied to primordial stem cell research.[58]
- Current restrictions on the creation of embryos would apply to stem cell research. This limit to scientific experimentation would take place without the benefit of public or scientific dialogue balancing the medical benefits of this research, in particular the promise of autologous transplantation, with the moral costs associated with the creation of embryos for

[54] See also *Tri-Council Statement* Art. 9D.
[55] *Proceed with Care*, at 1003.
[56] 1999 "Recent patents in stem cell research." *Nature Biotechnology* 17 April, 396.
[57] See above.
[58] See above.

research purposes. Such dialogue is necessary as these concerns are multi-faceted and public discourse indicates that opinions about the balancing of these issues are in a state of flux.

- No specific guidelines exist with respect to the importation of stem cells from other countries.
- No discussion of patenting issues with respect to stem cell lines or created embryos exists in this context. Restrictions on commercialisation of reproductive tissue may or may not be applicable to products of reproductive tissue.
- Given the financial potential of therapies developed from stem cell research and the influx of biotechnology funding into Canada from multi-national corporations, it is likely that differences between privately and publicly funded research will be created or exacerbated if privately funded researchers are not explicitly subject to the same standards as publicly funded-researchers. The situation in the United States, in which prohibitions in the public sphere serve as an expedient political response to controversial moral issues, while private research continues without similar guidelines should be avoided, especially where considerable moral consensus exists.
- No mechanism exists for tracking the progress of stem cell protocols to determine if the potential benefit promised is being delivered, if guidelines are being followed or whether different research models are warranted.

Another policy option related to the "Status Quo" option exists. It may be possible to expand, amend, and revise the current standards articulated by the voluntary moratorium and the *Tri-Council Statement* in order to clarify the ambiguities and overcome the difficulties noted above. The challenge for this option, however, is whether such an amendment process would adequately resolve these conflicts, provide the necessary clarity with respect to primordial stem cell research and yet maintain the integrity of the underlying documents. Nonetheless, with the influx of international biotechnology capital into Canada it will become increasingly important that privately funded researchers are held to enforceable legal standards of conduct in the future.

2. *Enact specific legislation with respect to stem cell oversight and guidance*

While this option has the benefit of addressing specific issues not currently addressed in the voluntary moratorium and the *Tri-Council Statement* it has significant drawbacks as a method of creating science policy. *Ad hoc* legislation in the field of ART leads to inconsistencies in policy, does not make clear the ethical commitments a society has in developing science policy, and is reactive in nature rather that proactive. This latter quality leads to an inability to create flexible and consistent policy, which addresses like cases alike and anticipates scientific developments within the field.[59]

3. *Enact a broad scheme of regulation which addresses ARTs, including embryo research, and within that framework address the scientific, ethical and social issues raised by primordial stem cell research*

This option is the preferred option, although it generally requires both a longer process and broader vision than either of the preceding options. This was the recommendation of the Royal Commission. In the area of embryo research, national and local regulation has several advantages over guidelines that apply only to those institutions receiving federal money. Leaving oversight of protocols to local REBs does not promote consistency, nor do most REBs have the time or expertise to create ethical and scientific guidelines for this research. National regulation in an area of moral controversy requires that the ethical commitments implicit in the decision to permit, restrict or prohibit certain research are explicit and are uniformly applicable.[60] Such transparency and consistency should be the goal of ART legislation, including regulation of primordial stem cell research. If a practice is morally suspect or incurs such moral costs that it should be prohibited, then there is little reason to permit such a practice in the private but not the public spheres. A system like the British system, which requires researchers to be licensed and research to be approved, ensures that a society's ethical commitments are being respected uniformly.

A regulatory scheme rather than one based on the criminal law permits greater flexibility and discussion. For example, where subcommittees are responsible for overseeing various scientific research protocols in a given area of research, those subcommittees will develop specific expertise and can be entrusted with discretionary authority. Mechanisms for tracking research protocols, ensuring that the creation of embryos or use of stem cells is necessary can be part of the mandate of the responsible authority. In addition, a regulatory scheme can be created which enables research aimed at new ends or of a different type to be added through amendment to regulations, rather than introducing new legislation or repealing overly restrictive legislation.

In this respect the Royal Commission remains the single greatest source of policy guidance with respect to drafting thorough, thoughtful ART policy. Clearly the Commission's recommendations would have to be updated to accommodate scientific developments in primordial stem cell research. Guidance is clearly also available in examining the approach taken in the United Kingdom. For example, the *Warnock report* adopted the following recommendation strategy:

- Frame recommendations in general terms, leaving matters of detail to be worked out by government;

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[59] A fuller discussion of the role of law in science policy if available in Knowles, L.P. 2000 "Science Policy and the Law: Reproductive and Therapeutic Cloning" in Legislating Morality: The Debate over Human Cloning, *N.Y.U. J. Legis. & Pub. Pol'y* Vol 4 No 1, 13-22.

[60] Shapiro, HT. 1999. Reflections on the interface of bioethics, public policy, and science. *Kennedy Institute of Ethics Journal*. 9(3): 209-22.

- Indicate what should be matters of good practice;
- Indicate what recommendations, if accepted, would require legislation, and
- Any proposed changes apply equally through the UK.[61]

With respect to embryo research and stem cell derivation and use, guidance on framing the issues involved can be found by examining the commonalities in guiding principles and recommendations strategies outlined by other countries. In making decisions about using embryos in research or ART, most national commissions adopted a long-term vision. This means that recommendations should be drafted in general terms and allow for flexibility and adaptability in the face of future developments.

Conclusion

Although the responses of the various groups and regions examined are diverse, one can discern a few points of emerging consensus. It seems clear that the question of ethical acceptability of EG cell research is less controversial than ES cell research. It is also apparent that the question of the acceptability of ES cell research is intimately bound up with the issue of embryo research. In general, where embryo research is permitted for some purposes, the use of spare embryos for ES cell research is deemed appropriate. There is little agreement on the acceptability of creating embryos for research and relatively little support for the creation of embryos using SCNT at this time. Most countries express both a desire to create policy that specifically addresses primordial stem cell research, and a desire to regulate that research in a careful and on-going fashion so as to gage the research outcomes. Concerns about informed consent, the health and safety of women and confidentiality are also integral to creating stem cell policy.

The Canadian government is faced with an opportunity to build upon the thoughtful work of both the Royal Commission and the three research councils in responding to the advent of primordial stem cell research. Should the government decide to create policy in this area, there is significant wisdom in analyzing the response of countries with similar cultural backgrounds and legal traditions. It is to be hoped that there will be a thoughtful and balanced response from the Canadian government that respects the principals articulated in the Royal Commission, including respect for human life and dignity and respect for women.

Appendix

Numbers in brackets refer to page in document where event is discussed.

Noteworthy Events shaping Primordial Stem Cell Policy in The United States:

November 1998
I. Announcements of ES and EG cell breakthroughs (2)
II. NBAC charged by President Clinton to study and report on ethical issues and policy directions in stem cell research (5,6)

January 1999
I. NIH director issues moratorium on NIH-funded research using pluripotent stem cells pending examination of the law (5)
II. NIH legal opinion issued (5)

September 1999
I. NBAC report published endorsing partial lifting of embryo research ban (6-8)

December 1999
II. NIH draft guidelines published (public comment period follows) (8)

August 2000
III. NIH final guidelines published, January 1999 moratorium lifted (8-12)

Noteworthy Events shaping Primordial Stem Cell Policy in The United Kingdom

November 1998
IV. Announcements of ES and EG cell breakthroughs in United States (2)

December 1998
V. HFEA/HGAC publishes recommendations for expanding embryo research to include research aims of primordial stem cell research (13-14)

July 1999
VI. Expert Group struck to study need for, benefits and risks of therapeutic cloning (14)

April 2000
VII. Nuffield Council report endorses HFEA/HGAC recommendations (14)

May 2000
VIII. Expert Panel (Donaldson) Report submitted to British government (14-15)

August 2000
IX. Government response endorsing recommendations published (16)

December 2000
X. Parliamentary free vote passes regulations by a large majority (16)

[61] The *Warnock Report*, pp. 6-7.