Human Stem Cell Research: Opportunities for Health and Ethical Perspectives

A Discussion Paper

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FOREWORD

Stem cell research holds great potential for the treatment of a number of serious conditions, including Alzheimer's and Parkinson's diseases, diabetes and spinal cord injuries. Over the last several years, there has been a virtual explosion of science that has prompted great excitement in the research and lay communities, as well as concerns around the ethical issues raised by the science. Guidelines in this area of research are essential to reassure the Canadian public and scientists that embryonic stem cell research will be undertaken within a well-defined and broadly accepted ethical and legal framework.

When the Government of Canada created the Canadian Institutes of Health Research (CIHR), Parliamentarians had a bold vision for more than a funding agency for all facets of health research in Canada; one that would proactively address emerging health opportunities, accelerate the discovery and implementation of new treatments, foster the discussion of ethical principles and lead to the development of guidelines for health researchers and their research.

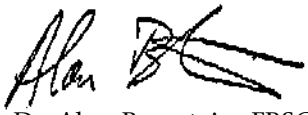
During CIHR's short history, we have established 13 Institutes and appointed Scientific Directors supported by Institute Advisory Board members of the highest calibre. As well, we have established a number of Working Groups to guide the Governing Council in making decisions in broad areas such as ethics, funding programs, peer review, privacy issues and embryonic stem cell research.

I am pleased to release the report of CIHR's Working Group on Stem Cells, led by Dr. Janet Rossant and a distinguished international team of experts in research, ethics and the law.

This is a discussion paper which we hope will generate comments from individuals and organizations. Such consultation will lead to a final report which will be presented to the Governing Council of CIHR for implementation as guidelines for funding human embryonic stem cell research.

I thank the members of the Working Group for their hard work, thoughtful advice and recommendations and am anxious to hear the views of Canadians on this promising area of health research.

Yours sincerely,



Dr. Alan Bernstein, FRSC
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EXECUTIVE SUMMARY

Stem cells, which are present in developing and adult animals, have the unique property of being able to either reproduce themselves (a process called "self-renewal") or differentiate into a variety of more specialized cells. Stem cells derived from early human embryos or cadaveric fetal tissue (embryonic stem [ES] cells or embryonic germ [EG] cells) have the greatest versatility (pluripotentiality) and ability to divide.

Human pluripotent stem cells have great research potential for the study of human reproduction and development, and for drug design and testing. However, their greatest impact may be as a source of cells that could be induced to differentiate into specialized cells or tissue for therapy in a wide variety of diseases and conditions such as Alzheimer's disease, Parkinson's disease, diabetes, kidney failure, heart disease, and spinal cord injury.

Stem cells with more a limited range of differentiation and growth potential have also been derived from a number of adult tissues. These may also be useful therapeutically and, although they are currently less versatile than ES and EG cells, they would have the advantage of minimizing immune rejection problems if derived from the patient. Recent studies showing that adult stem cells may have wider potential than was earlier thought have heightened interest in their possible therapeutic uses. Nevertheless, much basic research remains to be done before stem cells are sufficiently well understood for clinical applications to be considered.

Although stem cells' promise in the treatment of disease is enormous, the use of human embryonic and fetal tissue for research raises difficult ethical and legal issues. Canada provides no specific guidelines to researchers, research ethics boards (REBs), and funding agencies on how human pluripotent stem cells may be derived and used.

If Canadian researchers are to contribute to this area of study, they need guidance immediately. Accordingly, in the fall of 2000, CIHR established its ad hoc Working Group in Stem Cell Research to discuss issues relating to stem cell research in the context of current

Canadian policies and the worldwide situation, and to develop recommendations on how current policy can be applied to stem cell research.

This document highlights issues for CIHR to consider when developing its guidelines for stem cell research and funding policy. Given the nature of this consultation, we have not included an in-depth analysis of the various policy issues. Rather, the Working Group hopes that this document will clarify existing regulations and serve as a catalyst for further policy discussion.

The Working Group presents the following draft recommendations for discussion, emphasizing that any guidelines that CIHR adopts be regularly reviewed and revised.

1. Research on existing human embryonic stem cells and other human cells or cell lines of a pluripotent nature should be fundable by CIHR, subject to full ethical review and application of the relevant sections of the *Tri-Council Policy Statement* and other applicable legislation.[1]

2. Derivation, from human fetal tissue, of human germ cells and other human cells or cell lines of a pluripotent nature should be fundable by CIHR, subject to full ethical review and application of the relevant sections of the *Tri-Council Policy Statement* and other applicable legislation.

3. Research to derive human embryonic stem cells and other human cells or cell lines of a pluripotent nature from human embryos that remain after infertility treatments should be fundable by CIHR, subject to full ethical review and application of the relevant sections of the *Tri-Council Policy Statement* and other applicable legislation. Creation of human embryos by *in vitro* fertilization for the purpose of deriving stem cell lines should not be supported.

4. CIHR should place a moratorium on its funding of the following procedures:

i) creation of embryos by somatic cell nuclear transfer into human oocytes for the purpose of deriving stem cell lines

ii) research in which human pluripotent stem cells are utilized to create or contribute to human embryos

iii) research in which human pluripotent stem cells are combined with an animal embryo

iv) research in which animal pluripotent stem cells are combined with a human embryo.

5. A national oversight body should be established to provide ethical review of all publicly and privately funded human embryo, fetal tissue, and embryonic stem (ES) cell and embryonic germ (EG) cell research. Full ethical review should include review by both the local research ethics board and the national oversight body.

6. The *Tri-Council Policy Statement* should be reworked to take into account new areas of research on human embryos, fetal tissue, and ES and EG cells.

7. CIHR should participate in any discussion of federal regulations relating to human embryo, fetal tissue, and ES and EG cell research.

BACKGROUND

Biology of stem cells

Stem cells have a unique characteristic that distinguishes them from all other cell types derived from mammalian tissue: they have the ability to divide while maintaining their stem cell identity ("self-renewal"). In addition, in response to certain stimuli, they can differentiate to form more specialized cells.

Stem cells, which are found at different stages of mammalian development in a wide range of tissues, represent diverse populations with a wide range of biological features. Those with the greatest potential occur at the earliest stages of development, soon after the union of sperm and egg. They are called "totipotent" (capable of forming a new fetus and its associated membranes) or

"pluripotent" (capable of forming multiple tissues but not a complete organism). At the other end of the spectrum are stem cells that occur in adult organisms in tissues such as nerve, skin, and muscle. These appear to have a much more restricted range of differentiation than the pluripotent stem cells from early stages of development. However, adult stem cells have recently been found to have surprising plasticity—for instance, stem cells from bone marrow may give rise not only to blood cells but also to muscle, liver and neuron-like cells. Neural stem cells can give rise to blood and other cell types.

Scientists have been working with pluripotent stem cells derived from mouse embryos for over 20 years. Their studies have contributed much to learning about mammalian development, as well as to understanding of the role of specific genes, through the creation of mice engineered to have alterations in those genes.

A major scientific breakthrough occurred in 1998, when laboratories in the U.S. derived apparently pluripotent stem cells from human embryonic and fetal tissue. This advance opened the possibility of studying human development and identifying the factors that direct cell specialization. It also opened the way to developing better methods for evaluating drugs for efficacy and safety in a human model rather than in an animal one. Perhaps even more significantly, it opened the way to the possibility of cell therapy, in which stem cells could be grown *in vitro* and used to repair tissues that have degenerated or been destroyed. Pluripotent stem cells stimulated to produce a myriad of different specialized cell types could, in theory, be used to replace tissues destroyed by diabetes, heart disease, Alzheimer's disease, Parkinson's disease, retinal degeneration, muscular dystrophy, spinal cord injury, and so on, without the need for transplanted organs. Successful cell therapy could revolutionize the treatment of a wide range of injuries and degenerative diseases.

In order for this promise to be realized, scientists need to know more about the biological signals that direct differentiation, and methods must be found for growing large numbers of the desired type of cells. This will take time and will require the use of a wide

range of different stem cell types, including pluripotent ES and EG cells, which hold the greatest therapeutic promise because of their unlimited proliferative capacity and their ability to differentiate into virtually any tissue.

Issues relating to pluripotent stem cell use and derivation

In considering the advisability of research involving the use and derivation of pluripotent stem cells from human embryonic or fetal sources, many dimensions can be considered: clinical (therapeutic potential), scientific (advancement of knowledge and technologies associated with stem cells), economic (products and patents stemming from biotechnology), political (Canada's choice of position with respect to other countries), social (impact of the research and associated technologies on society; role of science and researchers; public input), and ethical (principles and values stemming from diverse beliefs, concepts of human nature, and "personhood").

In research involving pluripotent stem cell use and derivation, the ethical issues are the most contentious.

The ethical issues:

In principle, is human stem cell research ethically acceptable?

The most contentious ethical issue arising from stem cell research appears to be the derivation of embryonic or germcell–derived stem cells. These cells can be derived from:

- embryos created by *in vitro* fertilization that are no longer needed for fertility treatments
- embryos created from gametes specifically for research purposes
- fetal tissue resulting from elective abortions
- embryos created by somatic cell nuclear transfer (transfer of a nucleus from a somatic cell into an egg from which the nucleus has been removed).

All of these sources are contentious, and public opinion, shaped by diverse ethical, moral and religious traditions, is divided. With regard to the use of human embryos as a source of stem cells, some believe that the human embryo is a being with full moral status from the moment of conception and an inalienable right to life. In this view, the use of a human embryo for research purposes is morally unacceptable. Others consider that an early human embryo is just a collection of cells, its moral status equivalent to that of any other cells in the body. A middle ground confers upon the human embryo a special moral status because of its potential to develop into a human being. In this view, the human embryo has neither the full moral status of a person nor an absolute right to life. Though it has a right to protection, this right is not absolute and can be overridden; for example, by the possibility of a major benefit to other humans and to society in general. This latter view is the "graduated approach" expressed in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*,[1] in which permitted interventions correlate with the developmental stage of the embryo. This is the basis for the recommendation that research be permitted up to 14 days after formation of the zygote.

If human pluripotent stem cell research is, in principle, ethically acceptable, when is it in practice ethically acceptable?

If human embryonic stem cell research is to proceed, it should only do so in a responsible, ethical and accountable fashion. Of particular concern in this regard are: the source of the embryos used for research purposes, issues of informed choice (such as full disclosure and the absence of coercion and exploitation), privacy and confidentiality, and commercialization or profit motive. These issues are addressed in a generic fashion in the *Tri-Council Policy Statement*.

These guidelines, however, which were written prior to the derivation of the first human embryonic stem cells, do not provide specific guidance for research involving human ES and EG cells. We have not tried to address these issues in this paper. Rather, prior to drafting recommendations for CIHR, we would like to obtain the

views of researchers and the public in order to define questions in these areas that are specific to stem cell research and to formulate answers.

The regulatory situation in Canada

Researchers, REBs and funding agencies are currently unsure whether experiments involving the derivation and use of human ES and EG cells are eligible for federal funding, and, if they are, under what conditions. This is because although numerous documents have been published on reproductive and genetic technologies, there is no clear direction on stem cell research. A brief overview of documents relating to research with human subjects makes this point.

In 1978 the Medical Research Council published its first guidelines for research involving human subjects, updating them in 1987 in response to the emergence of new ethical problems. Ethical review committees for research involving human subjects have been required by the Medical Research Council since 1970, and standing committees known as research ethics boards (REBs) have been required at individual institutions since 1987. In 1989, the National Council on Bioethics in Human Research (now known as the National Council on Ethics in Human Research, or NCEHR) was established by the Medical Research Council (MRC) and the Royal College of Physicians and Surgeons, at the request of the MRC and with funding from the MRC and Health Canada, to provide support for the REBs (NCEHR sponsors now include the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada).

In 1994, recognizing that the distinctions among different research disciplines were becoming blurred, the three federal funding councils created a working group to develop an integrated set of ethical guidelines for research involving human subjects. Four years later, they released the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*.

The *Tri-Council Policy Statement* gives broad direction on the types of experimental procedures that may be done with human embryonic material.[2] Research on embryos no longer required for reproductive purposes may be ethically acceptable provided that certain conditions have been met, and research using fetal tissue is eligible for federal funding provided free and informed consent has been obtained and there is no directed donation. However, creating human embryos specifically for research purposes, ectogenesis (development of the embryo outside the womb), cloning human beings by somatic cell nuclear transfer, formation of animal–human hybrids, and transfer of embryos between humans and other species are not acceptable according to the *Tri-Council Policy Statement*.

The Royal Commission on New Reproductive Technologies was created in 1989 to examine the social, medical, legal, ethical, economic and research implications of new reproductive and genetic technologies. Its report issued in 1993 concludes that "the use of human zygotes in research can be considered acceptable when that research is directed to promoting understanding of human health and disease developing treatment," provided strict guidelines are followed. The report recommended establishing limits to the use of reproductive technologies through federal legislation, setting up a system for regulating acceptable technologies, and continued monitoring and response to new technologies as they emerge.

As a first step in regulating reproductive and genetic technologies, the federal government called for an interim voluntary moratorium in 1995 on a number of technologies clearly identified as contrary to the best interests of individuals and Canadian society. The following activities relating to human embryos are prohibited under the moratorium: sex selection for non-medical purposes; buying and selling of eggs, sperm and embryos; germ-line genetic alteration; ectogenesis (maintaining an embryo in an artificial womb); cloning of human embryos; creation of animal–human hybrids; retrieval of sperm or eggs from cadavers or fetuses for fertilization and implantation, or research involving the maturation of sperm or eggs outside the human body; and surrogacy arrangements.

The next step was taken in 1996 when Bill C-47 (*Human Reproductive and Genetic Technologies Act*), prohibiting certain practices, was introduced in Parliament. Based on the recommendations of the Royal Commission and on consultation with experts in the field, Health Canada added the following to the prohibited list: use of human sperm, eggs or embryos for assisted human reproduction procedures or for medical research without the informed consent of the donors; research on human embryos later than 14 days after conception; creation of embryos for research purposes only; and the making of an offer to provide or pay for prohibited services.

The Bill did not complete its legislative process because of the 1997 call for an election. Discussion continues about a legislative approach to regulating reproductive and genetic technologies, and it is anticipated that the Government of Canada will be putting in place a legislative framework that would encompass certain prohibited activities that Canadians deem unacceptable , while allowing the use of technologies that are acceptable but need to be regulated. A regulatory body could be created to develop standards for the use of reproductive materials in research and clinical practice, to issue licenses and ensure compliance, and to monitor emerging technologies.

Health Canada has been developing policies dealing with reproductive technologies since the late 1980s. There have been extensive consultations with groups representing stakeholders, the provinces and territories (because of overlapping jurisdictions in some aspects of health care), and with researchers and medical–legal experts. During this process of policy development, many ethical issues and some technologies relevant to human pluripotent stem cell research have been discussed. However, since the resulting documents were all published prior to the derivation of human stem cell lines in 1998, their relevance to human stem cell research has yet to be fully discussed.

At the moment, there is no specific guidance for researchers, research ethics boards, and funding agencies on how pluripotent stem cells may be derived and used. The only available documents are the *Tri-Council Policy Statement;* the 1995 moratorium; Health

Canada's 1996 publication entitled *New Reproductive and Genetic Technologies: Setting Boundaries, Enhancing Health;* and Bill C-47, which was never enacted. None of these specifically addresses issues relating to human pluripotent stem cells.

Thus, there is an urgent need for clear guidelines for stem cell research, guidelines that allow for response to rapidly moving research and shifting public opinion, and that ensure competent and efficient ethical and scientific oversight. In this way, Canadian stem cell researchers could remain at the forefront of their field, while conducting their research according to ethical standards.

The world-wide regulatory situation for stem cell research

A great deal of work has been done worldwide to establish the ethical framework for stem cell research. Expert working groups, in countries that include the U.S., the U.K., the Netherlands and Japan, have studied the issues, done extensive consultation, and produced legislation, regulatory frameworks, and research guidelines.

The United States

In the United States, the National Bioethics Advisory Committee (NBAC) issued a report in September 1999 (*Ethical Issues in Human Stem Cell Research*). The report recommends that:

i. Research involving the derivation and use of human ES cells from embryos remaining after infertility treatments should be eligible for federal funding. In adopting this recommendation, NBAC recognized a conflict with the ban that Congress imposed in 1995 in the appropriations bill for the Department of Health and Human Services, of which the National Institutes of Health (NIH) is a part. The ban prohibits use of federal funds to support any research in which a human embryo is destroyed. However, NBAC felt that the ban conflicted with ethical goals of medicine involving healing, prevention, and research and that it was important that federally funded researchers not be scientifically limited by having to rely on ES cells derived with private funds.

ii. Federal agencies should not fund research involving the derivation or use of human ES cells from embryos made solely for research purposes, either by *in vitro* fertilization (IVF) or using somatic cell nuclear transfer into oocytes.

After considering the NBAC report and following extensive public consultation, in August 2000 the National Institutes of Health issued guidelines for funding work with human pluripotent stem cells. If these guidelines stand, they will allow NIH-funded scientists to use previously derived embryonic or fetal stem cells after careful ethical review, and will establish a national oversight body. However, the use of NIH funds for research on human embryos (including those derived by nuclear transfer) would be prohibited. Thus, new stem cell lines cannot be derived from early embryos with NIH funds; they would have to be obtained from privately funded researchers who would be required to ensure that the lines were derived under strict provisions related to informed consent.

The United Kingdom

In the United Kingdom, the Human Fertilisation and Embryology Authority has regulated reproductive and genetic technologies since 1990. It has the power to regulate and license research and clinical practice, develop national standards of practice, and monitor compliance through the *Human Fertilisation and Embryology Act* (HFE Act), which defines the legal framework to carry out research on embryos. Under the HFE Act, a license must be obtained for creating embryos *in vitro* or carrying out research on embryos. Research was initially permitted only for the following purposes:

i. promoting advances in the treatment of infertility

ii. increasing knowledge about the causes of congenital disease

iii. increasing knowledge about the causes of miscarriages

iv. developing more effective techniques of contraception

v. developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.

In June 1999, the British Government created an Expert Group chaired by the Chief Medical Officerin response to the joint Human Fertilisation and Embryology Authority/Human Genetics Advisory Commission Report published in December 1998. The Group's role was to assess whether the list of purposes for which human embryos could be used in research should be extended to include stem cell research. Following input from the Nuffield Council on Bioethics and the Royal Society on the ethical, scientific and possible therapeutic aspects of stem cell research, the Group put forward, in April 2000, a number of recommendations, all subject to the controls in the *HFE Act*. These include the suggestion that research using embryos (whether created by *in vitro* fertilization or cell nuclear replacement) should be permitted in order to increase understanding about human disease and disorders and their cell-based treatments.

The Government accepted the Expert Group's recommendations and put forward, for debate and a free vote in both houses of Parliament, amendments expanding the purposes for which research licenses may be authorized to include:

vi. increasing knowledge about the creation and development of embryos

vii. increasing knowledge about disease

viii. enabling any such knowledge to be applied in developing treatments for disease.

The amendments to the *HFE Act* were passed in the House of Commons on December 18, 2000 and in the House of Lords on January 22, 2001, and took effect January 31, 2001. The *HFE Act*, which permits licensing of research in which human embryos are created for specific purposes, now effectively allows creation of embryos for the derivation of stem cells. Creation of embryos by somatic cell nuclear transfer is not prohibited under the *HFE Act*. In its report, the Chief Medical Officer's Expert Group recommended that the Human Fertilisation and Embryology Authority, when granting applications for licenses involving nuclear transfer, should be satisfied that the research could not be done in other ways.

In other parts of the world, guidelines and legislation offer less scope for derivation of and research with pluripotent stem cells derived from human embryos.

Continental Europe

In the Netherlands, a proposal for legislation on human embryo research was presented by the Government to the Lower House of the Dutch parliament in September 2000, following recommendations made by its Health Council. Under this proposed legislation, embryos not needed for fertility treatment could be used for scientific research, including the culturing of embryonic cells for medical, research and education purposes. The research must be approved by the Central Committee for Research Involving Human Subjects, must have a reasonable likelihood of providing new insights in the field of medical science, and must specifically require the use of embryos rather than a less invasive approach.

Despite the Health Council's recommendations, this legislation would not allow research with embryos created specifically for research. It is proposed, however, that the subject be reviewed in three to five years, at which time, if public opinion warrants, the ban may be lifted in specific cases. These would include research that is reasonably likely to lead to the identification of new insights in the fields of infertility, artificial reproduction techniques, congenital diseases, or transplant medicine, and can only be performed using specially created embryos.

In France, legislation passed in 1994 effectively prohibits any experimentation on embryos. However, since this law was passed, several official reports have been published suggesting revision of the law. A report by the French Parliament in 1998 draws a distinction between embryos intended for reproduction and those that are not going to be implanted. They propose that experiments may be carried out on the latter up to the 14th day, if the aim is to improve IVF techniques or create stem cell cultures needed for therapeutic development. Since it remains illegal to create embryos specifically for research, this experimentation and derivation could only apply to existing supernumerary ("spare") embryos.

The Council of State's 1999 report , drawn up at the request of the government, proposes authorizing research on embryos *in vitro*, subject to stringent rules, in light of the therapeutic prospects for stem cells raised by recent scientific discoveries.

Very recently, the French government has proposed changes to its 1994 bioethics law that would allow research on human embryos and facilitate the development of new therapies from work on embryonic stem cells. Researchers would be able to derive stem cells from "spare" embryos left over from *in vitro* fertilization procedures. The use of nuclear transfer technology would be allowed in order to develop therapeutic applications from embryonic stem cells.

Legislation in Austria and Germany is very restrictive. In Austria, donation of eggs and embryos is forbidden; cells may be examined and treated only so far as this is required for inducing a pregnancy; and there are no supernumerary embryos because the number of eggs fertilized in IVF treatments is limited. German embryo protection regulations are among the strictest in the world, forbidding research that harms an embryo, production of embryos for any purpose other than to start a pregnancy, and derivation of totipotent cells from an embryo for research or diagnosis. However, human embryo stem cell lines produced in other countries may be imported for research.

The laws in Scandinavia are more permissive. Denmark allows research on embryos if its goal is to improve IVF techniques. Finland allows licensed agencies to carry out medical research for a broad range of purposes on embryos up to 14 days after conception. However, the production of embryos for research purposes is forbidden. In Sweden, the objective of the research must be the improvement of infertility treatment; experiments for developing methods for genetic transformation of the embryo are not permitted. There is no explicit ban on creation of embryos for research. The government is currently reviewing its guidelines for stem cell and cloning research.

Belgium, Greece, Italy and Luxembourg currently have no legislation concerning human embryo research. However, in Belgium, conditions for IVF centres are determined by a Royal Decree of 1999 and a government proposal for regulation of embryo research will be discussed in the Belgian parliament within the next year or two. In Italy, legislation is proposed prohibiting the production of embryos for research, along with all non-therapeutic embryo research. However, a recent Reuters report indicates that Italy's Health Minister has given his support to a report by a group of scientific experts that supports the cloning of human embryos for derivation of stem cells for therapeutic purposes. All human embryo research is prohibited in Norway and Ireland.

The Council of Europe, composed of 41 states, including the 15 member states of the European Union, produced a Convention on Human Rights and Biomedicine in Oviedo, Spain in 1997. Countries ratifying this Convention are legally bound by its provisions unless they have conflicting legislation in place, in which case they may enter a reservation giving them the right not to apply certain provisions. The Convention includes provisions for "adequate protection of the embryo" in states that allow research on embryos, and prohibition of the creation of human embryos for research purposes. It has been ratified by a handful of countries, including Denmark, Greece and Spain.

Pacific nations

In Australia, The National Health and Medical Research Council issued the *Ethical Guidelines on Assisted Reproductive Technology* in 1996. These guidelines permit:

i. non-therapeutic research that does not harm the embryo

ii. research on human embryos that results in their destruction only in exceptional circumstances and with the approval of an Institutional Ethics Committee. (Exceptional circumstances require the likelihood of significant advances in knowledge or improvements in therapeutic technologies.)

Somatic cell nuclear transfer to produce human embryos is prohibited by the *Guidelines*; however, the Australian Health Ethics Committee of the NHMRC recommends public debate on the distinction between cloning whole individuals and copying parts of human tissue and cells. Legislation is done at the state level, and the Australian health ministers acknowledged in July 2000 the importance of developing a consistent national legislative approach to embryo research.

The Japanese Parliament enacted the *Human Cloning Regulation Act* on November 30, 2000. This act recommends allowing embryonic stem cell research but would prohibit cloning of people. The human embryo research subcommittee in the Life Ethics Committee of the Council for Science and Technology has prepared draft guidelines for research with ES cells. These have been posted on the Internet (in Japanese only) and will be considered in the preparation of a final report, which is expected this spring. All research will be required to conform to these guidelines.

Issues in Pluripotent Stem Cell research

The Working Group gave particular attention to five major scientific issues in stem cell research, and developed the following draft recommendations. The discussion was informed by the Working Group's current understanding of the scientific and health care potential of stem cell research, by legal and ethical issues, and by the background of national practice and policy and international comparisons. Discussion points a) to e) outlined below should be viewed in the context of the following recommendation:

Recommendation for Ongoing Review

Given the advances that are occurring in stem cell research, the changes in the legislative and regulatory environment in Canada and elsewhere in the world, and the evolution of public opinion in response to scientific and clinical developments, guidelines should not be static. CIHR should review the field of stem cell research on

an ongoing basis in order to be able to respond to future needs and discoveries from animal-based research, to broaden or narrow the scope of permitted research as appropriate, and to redraft the guidelines if they become outdated.

a) Should CIHR fund research with existing human embryonic stem cell lines?

DISCUSSION

Canada has many excellent stem cell researchers whose expertise could help explore the possible therapeutic value of human pluripotent stem cell lines. Currently there are few pluripotent stem cell lines available and their analysis has been restricted largely to privately funded research. These cell lines, if made available to researchers in Canada, would not carry any information could identify the original donors, so privacy and confidentiality need not be a concern. Though there may still be concerns regarding the nature of the informed consent from the original gamete donors, the use of these cell lines does not seem to be precluded.

Generally speaking, work with existing established immortalized human cell lines is not subject to ethical review in Canada, unless the experimentation itself raises additional ethical issues that would trigger the formal REB process. However, in view of the sensitivity about human ES cells, and the issues of the original informed consent for their derivation, if research on such lines is permitted, then **all** research protocols should be subject to full ethical review. Such review should include a careful evaluation of the informed consent conditions under which the cell line was derived, to ensure that the conditions are congruent with Canadian guidelines as set out under the relevant sections of the *Tri-Council Policy Statement* (TCPS) (sections 2, 3, 9, and10).

Recommendation

Research on existing human embryonic stem cells and other human cells or cell lines of a pluripotent nature is currently not precluded from CIHR funding. Such research should be fundable by CIHR, but all research proposals would be subject to full ethical review, with particular regard to consent and privacy and confidentiality issues. Particular note should be made of the relevant sections of the *Tri-Council Policy Statement* (sections 2, 3, 9, and 10) and any other applicable legislation.

b) Should CIHR fund research to derive new embryonic germ cells and other cell lines of a pluripotent nature from fetal material?

DISCUSSION

Research on existing human pluripotent stem cell lines will not be sufficient to fully understand and explore the potential of such lines. It will be important to discover how cell lines vary, how stable the pluripotent phenotype is, and how susceptible cell lines are to differences in derivation and maintenance conditions. EG cells that are apparently pluripotent have been derived from fetal gonad material but by only one lab. In addition, fetal stem cells from other tissues, such as the nervous system and the hematopoietic system, may have more proliferative and pluripotent capacity than adult stem cells and therefore need to be studied in more detail.

Currently, CIHR is funding a number of Canadian research projects, on various aspects of fetal development, that utilize human fetal material resulting from elective abortions.

Nevertheless, ethical, social and legal uncertainties remain. These include the moral and legal status of fetal tissue and the proper approach for obtaining informed consent. These and other issues warrant ongoing consideration. In the meantime, however, existing guidelines and regulations would permit, and the scientific and health care potential would justify, the derivation of pluripotent cell lines from fetal tissue.

The *Tri-Council Policy Statement* contains provisions that are relevant to research on fetal tissue,[3] although they were developed before many of the recent stem cell advances. Research projects using fetal tissue are eligible for funding, provided they meet applicable scientific and ethical standards, including free and informed consent with no intervention that would compromise the woman's decision on whether or not to continue the pregnancy, and no directed donation.

Recommendation

Research to derive and study human germ cells and other human cells or cell lines of a pluripotent nature from human fetal tissue for future therapeutic purposes should be fundable by CIHR. All such research proposals would be subject to full ethical review, with particular regard to consent and privacy and confidentiality issues. Particular note should be made of the relevant sections of the *Tri-Council Policy Statement* (especially section 9D) and any other applicable legislation.

c) Should CIHR fund research to derive new embryonic stem cells and other cell lines of a pluripotent nature from human blastocysts?

DISCUSSION

Research in rodents has suggested that embryonic stem cells derived from blastocysts, rather than from fetal gonads, may be a preferable source of pluripotent cell lines in terms of potential and absence of possible imprinting issues. "Spare" IVF-derived embryos that will not be used for reproductive purposes are potentially available for research. These are currently kept in a frozen state, discarded, or used for research in non–stem cell areas.

While the Working Group recognized that some people believe that all such embryos should be considered potential persons and therefore protected against destruction, it was felt that many couples would support the use of their "spare" embryos for stem cell

derivation, given the potential therapeutic good. Clearly, informed consent issues are paramount and any potential coercion to donate embryos for such purposes must be avoided.

Only embryos no longer required for reproductive purposes should be used. Given the major practical and ethical concerns with creating embryos for research purposes only, fertilization of eggs *in vitro* specifically to provide embryos for stem cell research, which contradicts the 1995 moratorium, should not be pursued.

Recommendation

Research to derive human embryonic stem cells and other human cells or cell lines of a pluripotent nature from human embryos that remain after infertility treatments should be fundable by CIHR. All such research proposals would be subject to full ethical review, with particular regard to consent and privacy and confidentiality issues. Particular note should be made of the relevant sections of the *Tri-Council Policy Statement* (especially Section 9) and any other applicable legislation. There are no convincing arguments at present for creating human embryos by *in vitro* fertilization for the purpose of deriving such stem cell lines.

d) Should CIHR fund research involving somatic cell nuclear transfer?

DISCUSSION

One of the practical issues related to the possible use of stem cells for replacement therapy for degenerative diseases is the problem of the immune system's rejection of the "foreign" cells. Ideally, in order to prevent rejection, the genes of the stem cells should be identical to those of the transplant recipient. One possible way to achieve this would be to take a nucleus from a cell of the transplant recipient, introduce it into a donated oocyte, from which the nuclear DNA had been removed, and allow the introduced nucleus to direct development of the egg. This is "somatic cell nuclear

transfer" or cloning technology. Derivation of ES cells from blastocysts created by nuclear transfer would theoretically allow generation of cells genetically identical to those of the recipient, for therapeutic purposes.

Embryos derived by somatic cell nuclear transfer could also be transferred to the uterus of a woman, with the intent of producing offspring genetically identical to the nuclear donor. This technique has been used successfully in a number of animal species, but has been almost universally condemned for humans.

Enormous technical and safety issues are inherent in the development and therapeutic application of nuclear transfer technology in humans. The efficiency of somatic cell nuclear transfer is very low, even in non-human mammals, and the normal development of embryos and cell lines derived in this manner is uncertain. How nuclear transfer reprograms the nuclear DNA, as well as how this knowledge might be applied to stem cell research, is currently best examined in non-human systems. Furthermore, many basic issues of the therapeutic potential of human ES cells need to be explored before any possible direct application of nuclear transfer technology could be envisaged. A moratorium on CIHR funding of somatic cell nuclear transfer in humans would be consistent with draft policy in most other parts of the world, except for the U.K., the Netherlands, and now possibly France (see "Continental Europe," above), which have left the door open to the possibility of this type of research when there is no other reasonable alternative.

Recommendation

CIHR should place a moratorium on its funding of research involving somatic cell nuclear transfer into human oocytes for the purpose of developing stem cell lines. CIHR should retain its prohibition, articulated in the 1995 moratorium, on research involving somatic cell nuclear transfer into human oocytes for the purpose of creating whole human beings,.

e) What conditions should be imposed on experimentation with cell lines of a pluripotent nature, once derived?

DISCUSSION

Although the study of human pluripotent stem cell development, differentiation and therapeutic applications should be supported, certain kinds of experiments in which cell lines maintained in culture are reintroduced into the embryonic environment to create genetically mosaic embryos (mixtures of cells from the host embryo and the donor cell line) are ethically problematic. We propose a moratorium on CIHR funding of the kinds of experiments listed below; however, we recognize that there is a need for more discussion and definition on this topic.

Recommendation

CIHR should place a moratorium on its funding of the following procedures:

- research in which human pluripotent stem cells are utilized to create or contribute to a human embryo
- research in which human pluripotent stem cells are combined with an animal embryo
- research in which animal pluripotent stem cells are combined with a human embryo.

DISCUSSION OF THE ETHICS REVIEW PROCESS

Under the current system, ethical review of the kind of research under discussion would occur at the level of local research ethics boards through the usual approval and reporting process using the guidelines laid out in the *Tri-Council Policy Statement*. However, this could be problematic in the sensitive area of human ES and EG cell research. First, the *Tri-Council Policy Statement* does not specifically address issues related to ES and EG cell research. Second, the quality of local review would not be uniform across the country, since capacity and expertise would vary from one centre to another. Third, this system would not assure accountability to the public and protection for the scientist.

Local research ethics boards need immediate guidance in dealing with applications for stem cell research projects; the proposed national oversight body (see below) would also need such national standards. While our final report will suggest how to deal with matters relating to consent, disclosure, privacy and confidentiality, and reimbursement of expenses, these issues urgently need more thorough debate, not only regarding stem cell research but also for other new areas of research. We suggest that CIHR immediately initiate such a discussion.

To avoid regional disparity and to establish proper accountability to the Canadian public, review and oversight at a national level should supplement the ethics review by local REBs. The oversight body would provide a national ethical perspective in this two-step ethics review of research involving human embryos and stem cells, while local review boards would ensure that the proposed research was consistent with community values.

The oversight body would need a full range of expertise, be devoid of conflict of interest, show integrity, and be accountable to the Canadian public. Initially this board could be established at CIHR, but in the long term an arms-length body should be created to perform this task. It would be set up through a transparent process to give it credibility.

The Working Group hopes that this ethical review would apply not only to federally funded research but also to research done privately (though we recognize that the current regulatory framework limits CIHR's jurisdiction in this context). Privately funded researchers should be encouraged to submit their research protocols for approval to the national oversight body. This approval could then become the accepted standard for legitimacy of all research involving embryos.

It is noteworthy that the *Guidelines for Research on Somatic Cell Gene Therapy in Humans*, published by the Medical Research Council of Canada in 1990, highlights the same potential difficulty of obtaining adequate local review of complex scientific and ethical

issues. This report also suggests two-tier review, with a national review committee providing scientific and ethical expertise and ensuring uniformity of review across the country.

A number of countries already have in place, or have proposed, a national oversight body for reproductive technologies in general. In the U.K., research can be pursued only under the aegis of the *Human Fertilisation and Embryology Act*, with a license granted by the Human Fertilisation and Embryology Authority (HFEA). The HFEA must be satisfied that the research project is necessary and desirable. The Chief Medical Officer's August 2000 report recommended that, in addition, an appropriate body should continue to monitor research projects to establish whether the research is delivering the anticipated results, as well as to highlight any unforeseen concerns. The Embryos Bill before the Dutch Parliament would require approval of research projects by the Central Committee on Research Involving Human Subjects (CCMO), established in December 1999. The proposed *NIH Guidelines* in the U.S. would create a Human Pluripotent Stem Cell Review Group (HPSCRG) to review proposals for the use of human pluripotent stem cells for compliance to the guidelines.

Local REBs and the proposed Canadian national oversight body would require guidance on procedures that should be followed in providing source materials for research on pluripotent ES and EG cells. These should be set out in a revised version of the Tri-Council statement that takes into account recent advances in stem cell research and other emerging areas of human biology. Although the Working Group's mandate is to provide advice only to CIHR, a consistent policy should apply to all three federal funding agencies.

Health Canada is committed to setting up a regulatory framework for assisted reproductive technologies that will include regulation of stem cell research. Procedures relating to provision of source materials and types of experiments that are permissible will be subject to regulation and perhaps licensing. The Working Group believes that CIHR, as the funding agency with the most expertise in research on embryos, fetal tissue, and pluripotent stem cells, should be actively involved in the discussions to establish federal regulations.

Recommendations:

- A national oversight body should be established to provide ethical review, in addition to that provided by local REBs, of all publicly and privately funded research on human embryos, fetal tissues, and ES and EG cells. Full ethical review should include ethics review by both the local research ethics boards and by the national oversight body.
- A reworking of the *Tri-Council Policy Statement*, particularly sections 9 and 10, should be undertaken to take into account new areas of human embryo, fetal tissue, ES and EG cell research.
- CIHR should participate actively in any discussion of federal regulations regarding human embryo, fetal tissue, and ES and EG cell research.

ENDNOTES:

[1] *The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* was published in August 1998 by the three federal research funding agencies: Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. It is intended to promote the highest ethical standards in research involving humans, and researchers and institutions applying for funding (or continued funding) must certify compliance with this policy.

[2] The *Tri-Council Policy Statement* position on research involving human embryos is as follows:

Article 9.4: It is not ethically acceptable to create human embryos specifically for research purposes. However, in those cases where human embryos are created for reproductive purposes, and subsequently are no longer required for such purposes, research involving human embryos may be considered to be ethically acceptable, but only if all of the following apply:

(a) The ova and sperm from which they were formed are obtained in accordance with Articles 9.1 and 9.2*;

(b) The research does not involve the genetic alteration of human gametes or embryos;

(c) Embryos exposed to manipulations not directed specifically to their ongoing normal development will not be transferred for continuing pregnancy; and

(d) Research involving human embryos takes place only during the first 14 days after their formation by combination of the gametes.

Article 9.5: It is not ethically acceptable to undertake research that involves ectogenesis, cloning human beings by any means including somatic cell nuclear transfer, formation of animal/human hybrids, or the transfer of embryos between humans and other species.

*** Article 9.1:** Researchers shall obtain free and informed consent from the individual whose gametes are to be used in research.

Article 9.2: In research, it is not ethical to use ova or sperm that have been obtained through commercial transactions, including exchange for service.

[3] The *Tri-Council Policy Statement* position on research involving fetal tissue is as follows:

Research involving the use of fetal tissue should be guided by respect for the woman's dignity and integrity. Researchers should thus obtain the free and informed consent of the woman whose fetal tissue is to be used for research. As a corollary of such respect, it is unacceptable to undertake research interventions that compromise the woman's decision on whether or not to continue her pregnancy. A former minister of Health, responding to a question concerning the transplantation into patients of tissues obtained from elective abortions, stated that he would not approve federal funding for such a procedure. The Royal Commission on New Reproductive Technologies has recommended that "Research

projects using fetal tissue (including those related to transplantation in human beings) be eligible for funding by the Medical Research Council of Canada and other public agencies, provided they meet applicable ethical and scientific research standards and tissue is obtained in accordance with the recommendations of the Royal Commission on New Reproductive Technologies." These recommendations include the establishment of a well-defined regulatory and licensing structure.

There are few absolutes in areas such as these, where ethical deliberation and societal values continue to evolve rapidly. Hence, while a woman's autonomy to consent to the use of her fetal tissue shall be respected, countervailing ethical considerations hold that a woman should not direct the use of such tissue to particular individuals, such as choosing to have fetal tissue used for Parkinson's disease research in a relative. The objection is based on concerns that the fetus not be used simply as a source of tissue but should be recognized as a potential person deserving of respect.

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