ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH

VOLUME I

Report and Recommendations of the National Bioethics Advisory Commission

Rockville, Maryland
September 1999

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a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

   1) the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and

   2) applications, including the clinical applications, of that research.

b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.

c) NBAC shall not be responsible for the review and approval of specific projects.

d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council.

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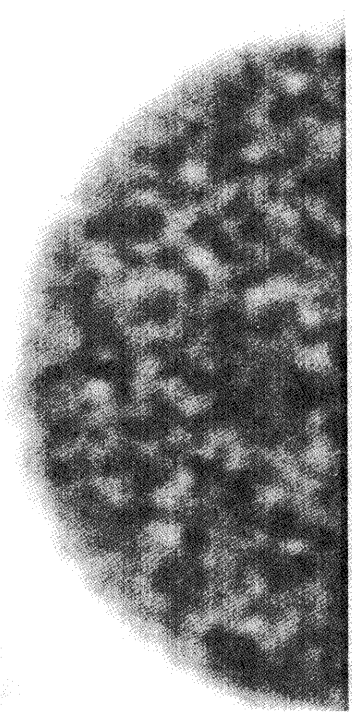

Rockville, Maryland
September 1999

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The President
The White House
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September 7, 1999

Dear Mr. President:

On November 14, 1998, you wrote to the National Bioethics Advisory Commission requesting that we "conduct a thorough review of the issues associated with...human stem cell research, balancing all medical and ethical issues." Your request came in response to reports of the successful isolation and culture of these specialized cells, which have simultaneously offered hope of new cures to debilitating and even fatal illness while renewing an important national debate about the ethics of research involving human embryos and cadaveric fetal material. After nine months of careful study, I am pleased to inform you that we have completed our deliberations and now provide you with the Commission's report, *Ethical Issues in Human Stem Cell Research.*

The Commission considered a broad set of scientific, medical, and legal issues, but focused particular attention on the ethical questions relevant to federal sponsorship of research involving human embryonic stem (ES) cells and embryonic germ (EG) cells. In our deliberations, we benefited greatly from the testimony of scientists, religious scholars, ethicists, lawyers, and the public, which testimony fully reflected the wide diversity of moral perspectives on these issues that characterizes our nation. Although wide agreement exists that human embryos deserve respect as a form of human life, there is disagreement both on the form such respect should take and on the level of protection owed at different stages of embryonic development. Moreover, it was clear from the outset that no public policy or set of recommendations could fully bridge these disagreements and satisfy all the thoughtful moral perspectives that are held by members of the American public.

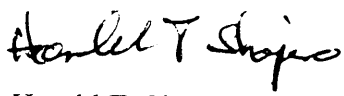
The Commission proposes 13 recommendations in several areas. Perhaps the most important recommendations reflect the Commission's view that federal sponsorship of research that involves the derivation and use of human embryonic stem (ES) cells and human embryonic germ (EG) cells should be limited in two ways. First, such research should be limited to using only two of the current sources of such cells; namely, cadaveric fetal material and embryos remaining after infertility treatments. Second, that such sponsorship be contingent on an appropriate and open system of national oversight and review.

Other recommendations address the requirements for consent from women or from couples who donate cadaveric fetal tissue or embryos remaining following infertility treatments; restrictions on the sale of fetal tissue or embryos and limits on the designation of those who may benefit from their use; the role of federal agencies in the review of research; and the encouragement of the private sector to comply with the same requirements recommended for federally funded researchers.

Taken together, we believe that these recommendations offer a policy framework that will provide the public with the assurance that important, potentially life-saving research can be conducted with federal sponsorship within a publicly accountable and rigorous system of oversight and review.

I would like to thank my fellow Commissioners, whose spirit of public service enabled them to work tirelessly to ensure that our report and its recommendations fully respected the moral worth of a wide variety of thoughtful viewpoints on the issues before us. We appreciate the opportunity to submit this report to you.

Sincerely,



Harold T. Shapiro
Chair

National Bioethics Advisory Commission

*To avoid the appearance of a conflict of interest, Commissioner Charo recused herself from all Commission deliberations as of February 1, 1999. She neither dissents from nor endorses this report and its recommendations.

**To avoid the appearance of a conflict of interest, Commissioner Greider recused herself from Commission deliberations as of July 19, 1999.

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*Until May 1999
**Until July 1999

Executive Summary

Introduction

In November 1998, President Clinton charged the National Bioethics Advisory Commission with the task of conducting a thorough review of the issues associated with human stem cell research, balancing all ethical and medical considerations. The President's request was made in response to three separate reports that brought to the fore the exciting scientific and clinical prospects of stem cell research while also raising a series of ethical controversies regarding federal sponsorship of scientific inquiry in this area. Scientific reports of the successful isolation and culture of these specialized cells have offered hope of new cures for debilitating and even fatal illness and at the same time have renewed an important national debate about the ethics of research involving human embryos and cadaveric fetal material.

Scientific and Medical Considerations

The stem cell is a unique and essential cell type found in animals. Many kinds of stem cells are found in the body, with some more differentiated, or committed, to a particular function than others. In other words, when stem cells divide, some of the progeny mature into cells of a specific type (e.g., heart, muscle, blood, or brain cells), while others remain stem cells, ready to repair some of the everyday wear and tear undergone by our bodies. These stem cells are capable of continually reproducing themselves and serve to renew tissue throughout an individual's life. For example, they constantly regenerate the lining of the gut, revitalize skin, and produce a whole range of blood cells. Although the term *stem cell* commonly is used to refer to the cells within the adult organism that renew tissue (e.g., hematopoietic stem cells, a type of cell found in the blood), the most fundamental and extraordinary of the stem cells are found in the early stage embryo. These *embryonic stem (ES) cells*, unlike the more differentiated adult stem cells or other cell types, retain the special ability to develop into nearly any cell type. *Embryonic germ (EG) cells*, which originate from the primordial reproductive cells of the developing fetus, have properties similar to ES cells.

It is the potentially unique versatility of the ES and EG cells derived, respectively, from the early stage embryo and cadaveric fetal tissue that presents such unusual scientific and therapeutic promise. Indeed, scientists have long recognized the possibility of using such cells to generate more specialized cells or tissue, which could allow the generation of new cells to be used to treat injuries or diseases, such as Alzheimer's disease, Parkinson's disease, heart disease, and kidney failure. Likewise, scientists regard these cells as an important—perhaps essential—means for understanding the earliest stages of human development and as an important tool in the development of life-saving drugs and cell-replacement therapies to treat disorders caused by early cell death or impairment.

The techniques for deriving these cells have not been fully developed as standardized and readily available research tools, and the development of any therapeutic application remains some years away. Thus, ES and EG cells are still primarily a matter of intense research interest.

At this time, human stem cells can be derived from the following sources:

- human fetal tissue following elective abortion (EG cells),

- human embryos that are created by *in vitro* fertilization (IVF) and that are no longer needed by couples being treated for infertility (ES cells),
- human embryos that are created by IVF with gametes donated for the sole purpose of providing research material (ES cells), and
- potentially, human (or hybrid) embryos generated asexually by somatic cell nuclear transfer or similar cloning techniques in which the nucleus of an adult human cell is introduced into an enucleated human or animal ovum (ES cells).

In addition, although much promising research currently is being conducted with stem cells obtained from adult organisms, studies in animals suggest that this approach will be scientifically and technically limited, and in some cases the anatomic source of the cells might preclude easy or safe access. However, because there are no legal restrictions or new ethical considerations regarding research on adult stem cells (other than the usual concerns about consent and risks), important research can and should go forward in this area. Moreover, because important biological differences exist between embryonic and adult stem cells, this source of stem cells should not be considered an alternative to ES and EG cell research.

Ethical and Policy Considerations

The scientific reports of the successful isolation and culture of ES and EG cells have renewed a longstanding controversy about the ethics of research involving human embryos and cadaveric fetal material. This controversy arises from sharply differing moral views regarding elective abortion or the use of embryos for research. Indeed, an earnest national and international debate continues over the ethical, legal, and medical issues that arise in this arena. This debate represents both a challenge and an opportunity: a challenge because it concerns important and morally contested questions regarding the beginning of life, and an opportunity because it provides another occasion for serious public discussion about important ethical issues. We are hopeful that this dialogue will foster public understanding about the relationships between the opportunities that biomedical science offers to improve human welfare and the limits set by important ethical obligations.

Although we believe most would agree that human embryos deserve respect as a form of human life, disagreements arise regarding both what form such respect should take and what level of protection is required at different stages of embryonic development. Therefore, embryo research that is not therapeutic to the embryo is bound to raise serious concerns and to heighten the tensions between two important ethical commitments: to cure disease and to protect human life. For those who believe that the embryo has the moral status of a person from the moment of conception, research (or any other activity) that would destroy the embryo is considered wrong and should not take place. For those who believe otherwise, arriving at an ethically acceptable policy in this arena involves a complex balancing of a number of important ethical concerns. Although many of the issues remain contested on moral grounds, they co-exist within a broad area of consensus upon which public policy can, at least in part, be constructed.

For most observers, the resolution of these ethical and scientific issues depends to some degree on the source of the stem cells. The use of cadaveric fetal tissue to derive EG cell lines—like other uses of tissues or organs from dead bodies—is generally the most accepted, provided that the research complies with the system of public safeguards and oversight already in place for such scientific inquiry. With respect to embryos and the ES cells from which they can be derived, some draw an ethical distinction between two types of embryos. One is referred to as the *research embryo*, an embryo created through IVF with gametes provided solely for research purposes. Many people, including the President, have expressed the view that the federal government should not fund research that involves creating such embryos. The second type of embryo is that which was created for infertility treatment, but is now intended to be discarded because it is unsuitable or no longer needed for such treatment. The use of these embryos raises fewer ethical questions because it does not alter their final disposition. Finally, the recent demonstration of cloning techniques (somatic cell nuclear transfer) in nonhuman animals suggests that transfer of a human somatic cell nucleus into an oocyte

might create an embryo that could be used as a source of ES cells. The creation of a human organism using this technique raises questions similar to those raised by the creation of research embryos through IVF, and at this time federal funds may not be used for such research. In addition, if the enucleated oocyte that was to be combined with a human somatic cell nucleus came from an animal other than a human being, other issues would arise about the nature of the embryo produced. Thus, each source of material raises ethical questions as well as scientific, medical, and legal ones.

Conscientious individuals have come to different conclusions regarding both public policy and private actions in the area of stem cell research. Their differing perspectives by their very nature cannot easily be bridged by any single public policy. But the development of public policy in a morally contested area is not a novel challenge for a pluralistic democracy such as that which exists in the United States. We are profoundly aware of the diverse and strongly held views on the subject of this report and have wrestled with the implications of these different views at each of our meetings devoted to this topic. Our aim throughout these deliberations has been to formulate a set of recommendations that fully reflects widely shared views and that, in our view, would serve the best interests of society.

Most states place no legal restrictions on any of the means of creating ES and EG cells that are described in this report. In addition, current Food and Drug Administration regulations do not apply to this type of early stage research. Therefore, because the public controversy surrounding such activities in the United States has revolved around whether it is appropriate for the federal government to sponsor such research, this report focuses on the question of whether the scientific merit and the substantial clinical promise of this research justify federal support, and, if so, with what restrictions and safeguards.

Conclusions and Recommendations

This report presents the conclusions that the Commission has reached and the recommendations that the Commission has made in the following areas: the ethical acceptability of federal funding for research that either derives or uses ES or EG cells; the means of ensuring appropriate consent of women or couples who donate cadaveric fetal tissue or embryos remaining after infertility treatments; the need for restrictions on the sale of these materials and the designation of those who may benefit from their use; the need for ethical oversight and review of such research at the national and institutional level; and the appropriateness of voluntary compliance by the private sector with some of these recommendations.

The Ethical Acceptability of Federal Funding of ES and EG Cell Research by the Source of the Material

A principal ethical justification for public sponsorship of research with human ES or EG cells is that this research has the potential to produce health benefits for individuals who are suffering from serious and often fatal diseases. We recognize that it is possible that the various sources of human ES or EG cells eventually could be important to research and clinical application because of, for example, their differing proliferation potential, differing availability and accessibility, and differing ability to be manipulated, as well as possibly significant differences in their cell biology. **At this time, therefore, the Commission believes that federal funding for the use and derivation of ES and EG cells should be limited to two sources of such material: cadaveric fetal tissue and embryos remaining after infertility treatments.** Specific recommendations and their justifications are provided below.

Recommendation 1: EG Cells from Fetal Tissue

Research involving the derivation and use of human EG cells from cadaveric fetal tissue should continue to be eligible for federal funding. Relevant statutes and regulations should be amended to make clear that the ethical safeguards that exist for fetal tissue transplantation also apply to the derivation and use of human EG cells for research purposes.

Considerable agreement exists, both in the United States and throughout the world, that the use of fetal tissue in therapy for people with serious disorders, such

as Parkinson's disease, is acceptable. Research that uses tissue from aborted fetuses is analogous to the use of fetal tissue in transplantation. The rationales for conducting EG research are equally strong, and the arguments against it are not persuasive. The removal of fetal germ cells does not occasion the destruction of a live fetus, nor is fetal tissue intentionally or purposefully created for human stem cell research. Although abortion itself doubtless will remain a contentious issue in our society, the procedures that have been developed to prevent fetal tissue donation for therapeutic transplantation from influencing the abortion decision offer a model for creating such separation in research to derive human EG cells. Because the existing statutes are written in terms of tissue transplantation, which is not a current feature of EG cell research, changes are needed to make it explicit that the relevant safeguards will apply to research to derive EG cells from aborted fetuses. At present, no legal prohibitions exist that would inhibit the use of such tissue for EG cell research.

Recommendation 2: ES Cells from Embryos Remaining After Infertility Treatments

Research involving the derivation and use of human ES cells from embryos remaining after infertility treatments should be eligible for federal funding. An exception should be made to the present statutory ban on federal funding of embryo research to permit federal agencies to fund research involving the derivation of human ES cells from this source under appropriate regulations that include public oversight and review. (See Recommendations 5 through 9.)

The current ban on embryo research is in the form of a rider to the appropriations bill for the Department of Health and Human Services (DHHS), of which the National Institutes of Health (NIH) is a part. The rider prohibits use of the appropriated funds to support any research "in which a human embryo [is] destroyed, discarded, or knowingly subjected to risk of injury greater than that allowed for research on fetuses *in utero*" (Pub. L. No. 105-78, 513(a)). The term "human embryo" in the statute is defined as "any organism . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells." The ban is revisited each year when the language of the NIH appropriations bill is considered.

The ban, which concerns only federally sponsored research, reflects a moral point of view either that embryos deserve the full protection of society because of their moral status as persons or that there is sufficient public controversy to preclude the use of federal funds for this type of research. At the same time, however, some effects of the embryo research ban raise serious moral and public policy concerns for those who hold differing views regarding the ethics of embryo research. In our view, the ban conflicts with several of the ethical goals of medicine and related health disciplines, especially healing, prevention, and research. These goals are rightly characterized by the principles of beneficence and nonmaleficence, which jointly encourage pursuing social benefits and avoiding or ameliorating potential harm.

Although some may view the derivation and use of ES cells as ethically distinct activities, we do not believe that these differences are significant from the point of view of eligibility for federal funding. That is, we believe that it is ethically acceptable for the federal government to finance research that both derives cell lines from embryos remaining after infertility treatments and that uses those cell lines. Although one might argue that some important research could proceed in the absence of federal funding for research that derives stem cells from embryos remaining after infertility treatments (i.e., federally funded scientists merely using cells derived with private funds), we believe that it is important that federal funding be made available for protocols that also derive such cells. Relying on cell lines that might be derived exclusively by a subset of privately funded researchers who are interested in this area could severely limit scientific and clinical progress.

Trying to separate research in which human ES cells are used from the process of deriving those cells presents an ethical problem, because doing so diminishes the scientific value of the activities receiving federal support. This separation—under which neither biomedical researchers at NIH nor scientists at universities and other research institutions that rely on federal support could participate in some aspects of this research—rests on the

mistaken notion that the two areas of research are so distinct that participating in one need not mean participating in the other. We believe that this is a misrepresentation of the new field of human stem cell research, and this misrepresentation could adversely affect scientific progress for several reasons.

First, researchers using human ES cell lines will derive substantial scientific benefits from a detailed understanding of the process of ES cell derivation, because the properties of ES cells and the methods for sustaining the cell lines may differ depending on the conditions and methods that were used to derive them. Thus, scientists who conduct basic research and are interested in fundamental cellular processes are likely to make elemental discoveries about the nature of ES cells as they derive them in the laboratory. Second, 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. Third, ES cells are not indefinitely stable in culture. As these cells are grown, irreversible changes occur in their genetic makeup. Thus, especially in the first few years of human ES cell research, it is important 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.

Thus, anyone who believes that federal support of this important new field of research should maximize its scientific and clinical value within a system of appropriate ethical oversight should be dissatisfied with a position that allows federal agencies to fund research using human ES cells but not research through which the cells are derived from embryos. Instead, recognizing the close connection in practical and ethical terms between derivation and use of the cells, it would be preferable to enact provisions applicable to funding by all federal agencies, provisions 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 programs.

Recommendation 3: ES Cells from Embryos Made Solely for Research Purposes Using IVF

Federal agencies should not fund research involving the derivation or use of human ES cells from embryos made solely for research purposes using IVF.

ES cells can be obtained from human research embryos created from donor gametes through IVF for the sole purpose of deriving such cells for research. The primary objection to creating embryos specifically for research is that there is a morally relevant difference between generating an embryo for the sole purpose of creating a child and producing an embryo with no such goal. Those who object to creating embryos for research often appeal to arguments about respecting human dignity by avoiding instrumental use of human embryos (i.e., using embryos merely as a means to some other goal does not treat them with appropriate respect or concern as a form of human life).

In 1994, the NIH Human Embryo Research Panel argued in support of federal funding of the creation of embryos for research purposes in exceptional cases, such as the need to create banks of cell lines with different genetic make-ups that encoded various transplantation antigens—the better to respond, for example, to the transplant needs of groups with different genetic profiles. This would require the recruitment of embryos from genetically diverse donors.

In determining how to deal with this issue, a number of points are worth considering. First, it is possible that the creation of research embryos will provide the only way in which to conduct certain kinds of research, such as research into the process of human fertilization. Second, as IVF techniques improve, it is possible that the supply of embryos for research from this source will dwindle. Nevertheless, we have concluded that, either from a scientific or a clinical perspective, there is no compelling reason at this time to provide federal funds for the creation of embryos for research. At the current time, cadaveric fetal tissue and embryos remaining after infertility treatment provide an adequate supply of research resources for federal research projects.

Recommendation 4: ES Cells from Embryos Made Using Somatic Cell Nuclear Transfer into Oocytes

Federal agencies should not fund research involving the derivation or use of human ES cells from embryos made using somatic cell nuclear transfer into oocytes.

Somatic cell nuclear transfer of the nucleus of an adult somatic cell into an enucleated human egg likely

has the potential of creating a human embryo. To date, although little is known about these embryos as potential sources of human ES cells, there is significant reason to believe that their use may have therapeutic potential. For example, the potential use of matched tissue for autologous cell replacement therapy from ES cells may require the use of somatic cell nuclear transfer. The use of this technique to create an embryo arguably is different from all the other cases we considered—due to the asexual origin of the source of the ES cells—although oocyte donation is necessarily involved. The Commission concludes that, at this time, federal funding should not be provided to derive ES cells from this source. Nevertheless, scientific progress and the medical utility of this line of research should be monitored closely.

Requirements for the Donation of Cadaveric Fetal Tissue and Embryos for Research

Potential donors of embryos for ES cell research must be able to make voluntary and informed choices about whether and how to dispose of their embryos. Because of concerns about coercion and exploitation of potential donors, as well as societal controversy about the moral status of embryos, it is important, whenever possible, to separate donors' decisions to dispose of their embryos from their decisions to donate them for research. Potential donors should be asked to provide embryos for research only if they have decided to have those embryos discarded instead of donating them to another couple or storing them. If the decision to discard the embryos precedes the decision to donate them for research purposes, then the research determines only how their destruction occurs, not whether it occurs.

Recommendation 5: Requirements for Donation to Stem Cell Research of Embryos That Would Otherwise Be Discarded After Infertility Treatment

Prospective donors of embryos remaining after infertility treatments should receive timely, relevant, and appropriate information to make informed and voluntary choices regarding disposition of the embryos. Prior to considering the potential research use of the embryos, a prospective donor should have been presented with the option of storing the embryos, donating them to another woman, or discarding them. If a prospective donor chooses to discard embryos remaining after infertility treatment, the option of donating to research may then be presented. (At any point, the prospective donors' questions—including inquiries about possible research use of any embryos remaining after infertility treatment—should be answered truthfully, with all information that is relevant to the questions presented.)

During the presentation about potential research use of embryos that would otherwise be discarded, the person seeking the donation should

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

To assure that inappropriate incentives do not enter into a woman's decision to have an abortion, we recommend that directed donation of cadaveric fetal tissue for EG cell derivation be prohibited. Although the ethical considerations supporting a prohibition of the directed donation of human fetal tissue are less acute for EG cell research than for transplantation, certain concerns remain. Potential donors of cadaveric fetal tissue for EG cell derivation would not receive a direct therapeutic incentive to create or abort tissue for research purposes in the same way that such personal interest might arise in a transplant context. However, we agree that the prohibition remains a prudent and appropriate way of assuring that inappropriate incentives, regardless of how remote they may be, are not introduced into a woman's decision to have an abortion. Any suggestion of personal benefit to the donor or to an individual known to the donor would be untenable and possibly coercive.

Recommendation 6: No Promises to Embryo Donors That Stem Cells Will Be Provided to Particular Patient-Subjects

In federally funded research involving embryos remaining after infertility treatments, researchers may not promise donors that ES cells derived from their embryos will be used to treat patient-subjects specified by the donors.

Existing rules prohibit the practice of designated donation, the provision of monetary inducements to women undergoing abortion, and the purchase or sale of fetal tissue. We concur in these restrictions and in the earlier recommendation of the 1988 Human Fetal Tissue Transplantation Research Panel that the sale of fetal tissue for research purposes should not be permitted under any circumstances. The potential for coercive pressure is greatest when financial incentives are present, and the treatment of the developing human embryo or fetus as an entity deserving of respect may be greatly undermined by the introduction of any commercial motive into the donation or solicitation of fetal or embryonic tissue for research purposes.

Recommendation 7: Commerce in Embryos and Cadaveric Fetal Tissue

Embryos and cadaveric fetal tissue should not be bought or sold.

If and when sufficient scientific evidence and societal agreement exist that the creation of embryos specifically for research or therapeutic purposes is justified (specifically through somatic cell nuclear transfer), prohibitions on directed donation should be revisited. For obvious reasons, the use of somatic cell nuclear transfer to develop ES cells for autologous transplantation might require that the recipient be specified.

The Need for National Oversight and Review

The need for national as well as local oversight and review of human stem cell research is crucial. No such system currently exists in the United States. A national mechanism to review protocols for *deriving* human ES and EG cells and to monitor research using such cells would ensure strict adherence to guidelines and standards across the country. Thus, federal oversight can provide the public with the assurance that research involving stem cells is being undertaken appropriately. Given the ethical issues involved in human stem cell research—an area in which heightened sensitivity about the very research itself led the President to request that the Commission study the issue—the public and the Congress must be assured that oversight can be accomplished efficiently, constructively, and in a timely fashion, with sufficient attention to the relevant ethical considerations.

Recommendation 8: Creation and Duties of an Oversight and Review Panel

DHHS should establish a National Stem Cell Oversight and Review Panel to ensure that all federally funded research involving the derivation and/or use of human ES or EG cells is conducted in conformance with the ethical principles and recommendations contained in this report. The panel should have a broad, multidisciplinary membership, including members of the general public, and should

a) **review protocols for the derivation of ES and EG cells and approve those that meet the requirements described in this report,**

b) **certify ES and EG cells lines that result from approved protocols,**

c) **maintain a public registry of approved protocols and certified ES and EG cell lines,**

d) **establish a database—linked to the public registry—consisting of information submitted by federal research sponsors (and, on a voluntary basis, by private sponsors, whose proprietary information shall be appropriately protected) that includes all protocols that derive or use ES or EG cells (including any available data on research outcomes, including published papers),**

e) **use the database and other appropriate sources to track the history and ultimate use of certified cell lines as an aid to policy assessment and formulation,**

f) **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, and**

g) **report at least annually to the DHHS Secretary with an assessment of the current state of the science for both the derivation and use of human ES and EG cells, a review of recent developments in the broad category of stem cell research, a summary of any emerging ethical or social concerns associated with this research, and an analysis of the adequacy and continued appropriateness of the recommendations contained in this report.**

The Need for Local Review of Derivation Protocols

For more than two decades, prospective review by an Institutional Review Board (IRB) has been the principal method for assuring that federally sponsored research involving human subjects will be conducted in compliance with guidelines, policies, and regulations designed to protect human beings from harm. This system of local review has been subject to criticism, and, indeed, in previous analyses we have identified a number of concerns regarding this system. In the course of preparing this report, we considered a number of proposals that would allow for the local review of research protocols involving human stem cell research, bearing in mind that a decision by the Commission to recommend a role for IRBs might be incorrectly interpreted as endorsing the view that human ES or EG cells or human embryos are human subjects and therefore would be under the purview of the Common Rule.

We adopted the principle, reflected in these recommendations, that for research to derive human ES and EG cells, a system of national oversight and review supplemented by local review would be necessary to ensure that important research could proceed—but only under specific conditions. We recognized that for research proposals involving the derivation of human ES or EG cells, many of the ethical issues associated with these protocols could be considered at the local level, that is, at the institutions at which the research would be taking place. For protocols using but not deriving ES cells (i.e., generating the cells elsewhere), a separate set of ethical deliberations would have occurred. In general, the IRB is an appropriate body to review protocols that aim to derive ES or EG cells. Although few review bodies (including IRBs) have extensive experience in reviewing protocols of this kind, they remain the most visible and expert entities available. It is for this reason, for example, that we make a number of recommendations (8, 9, 10, 11, and 12) that discuss the importance of developing additional guidance for the review of such protocols.

For proposals involving the derivation of human ES or EG cells, particular sensitivities require attention through a national review process. This process should, however, begin at the local level, because institutions that intend to conduct research involving the derivation of human ES cells or EG cells should continue to take responsibility for assuring the ethical conduct of that research. More importantly, however, IRBs can play an important role, particularly by reviewing consent documents and by assuring that collaborative research undertaken by investigators at foreign institutions has satisfied any regulatory requirements for sharing research materials.

Recommendation 9: Institutional Review of Protocols to Derive Stem Cells

Protocols involving the *derivation* of human ES and EG cells should be reviewed and approved by an IRB or by another appropriately constituted and convened institutional review body prior to consideration by the National Stem Cell Oversight and Review Panel. (See Recommendation 8.) This review should ensure compliance with any requirements established by the panel, including confirming that individuals or organizations (in the United States or abroad) that supply embryos or cadaveric fetal tissue have obtained them in accordance with the requirements established by the panel.

Responsibilities of Federal Research Agencies

Federal research agencies have in place a comprehensive system for the submission, review, and approval of research proposals. This system includes the use of a peer review group—sometimes called a study section or initial review group—that is established to assess the scientific merit of the proposals. In addition, in some agencies, such as NIH, staff members review protocols prior to their transmittal to a national advisory council for final approval. These levels of review provide an opportunity to consider ethical issues that arise in the proposals.

When research proposals involve human subjects, federal agencies rely on local IRBs to review and approve the research in order to assure that it is ethically acceptable. (See Recommendation 9.) A grant application should not be funded until ethical issues that are associated with research involving human subjects have been resolved fully. Therefore, at every point in this continuum—from the first discussions that a prospective applicant may have with program staff within a particular institution to the final decision by the relevant national advisory council—ethical and scientific issues can be addressed by the sponsoring agency.

Recommendation 10: Sponsoring Agency Review of Research Use of Stem Cells

All federal agencies should ensure that their review processes for protocols using human ES or EG cells comply with any requirements established by the National Stem Cell Oversight and Review Panel (see Recommendation 8), paying particular attention to the adequacy of the justification for using such cell lines.

Research involving human ES and EG cells raises critical ethical issues, particularly when the proposals involve the derivation of ES cells from embryos remaining after infertility treatments. We recognize that these research proposals may not follow the paradigm usually associated with human subjects research. Nevertheless, research proposals being considered for funding by federal agencies must, in our view, meet the highest standards of scientific merit and ethical acceptability. To that end, the recommendations made in this report, including a proposed set of *Points to Consider in Evaluating Basic Research Involving Human ES Cells and EG Cells*, constitute a set of ethical and policy considerations that should be reflected in the respective policies of federal agencies conducting or sponsoring human ES or EG cell research.

Attention to Issues for the Private Sector

Although this report primarily addresses the ethical issues associated with the use of federal funds for research to derive and use ES and EG cells, we recognize that considerable work in both of these areas will be conducted under private sponsorship. Thus, our recommendations may have implications for those working in the private sector. First, for cell lines to be eligible for use in federally funded research, they must be certified by the National Stem Cell Oversight and Review Panel described in Recommendation 8. Therefore, if a private company aims to make its cell lines available to publicly funded researchers, it must submit its derivation protocol(s) to the same oversight and review process recommended for the public sector, i.e., local review (see Recommendation 9) and for certification that the cells have been derived from embryos remaining after infertility treatments or from cadaveric fetal tissue.

Second, we hope that nonproprietary aspects of protocols developed under private sponsorship will be made available in the public registry, as described in Recommendation 8. The greater the participation of the private sector in providing information on stem cell research, the more comprehensive the development of the science and related public policies in this area.

Third, and perhaps most relevant, in an ethically sensitive area of emerging biomedical research it is important that all members of the research community, whether in the public or private sectors, conduct the research in a manner that is open to appropriate public scrutiny. The last two decades have witnessed an unprecedented level of cooperation between the public and private sectors in biomedical research, which has resulted in the international leadership position of the United States in this arena. Public bodies and other authorities, such as the Recombinant DNA Advisory Committee, have played a crucial role in enabling important medical advances in fields such as gene therapy by providing oversight of both publicly and privately funded research efforts. We believe that voluntary participation by the private sector in the review and certification procedures of the proposed national panel, as well as in its deliberations, can contribute equally to the socially responsible development of ES and EG cell technologies and accelerate their translation into biomedically important therapies that will benefit patients.

Recommendation 11: Voluntary Actions by Private Sponsors of Research That Would Be Eligible for Federal Funding

For privately funded research projects that involve ES or EG cells that would be eligible for federal funding, private sponsors and researchers are

encouraged to adopt voluntarily the applicable recommendations of this report. This includes submitting protocols for the derivation of ES or EG cells to the National Stem Cell Oversight and Review Panel for review and cell line certification. (See Recommendations 8 and 9.)

In this report, we recommend that federally funded research to derive ES cells be limited to those efforts that use embryos remaining after infertility treatment. Some of the recommendations made in this context—such as the requirement for separating the decision by a woman to cease such treatment when embryos still remain and her decision to donate those embryos to research—simply do not apply to efforts to derive ES cells from embryos created (whether by IVF or somatic cell nuclear transfer) solely for research purposes, activities that might be pursued in the private sector. Nevertheless, other ethical standards and safeguards embodied in the recommendations, such as provisions to prevent the coercion of women and the commodification of human reproduction, remain vitally important, even when embryos are created solely for research purposes.

Recommendation 12: Voluntary Actions by Private Sponsors of Research That Would Not Be Eligible for Federal Funding

For privately funded research projects that involve deriving ES cells from embryos created solely for research purposes and that are therefore not eligible for federal funding (see Recommendations 3 and 4)

a) professional societies and trade associations should develop and promulgate ethical safeguards and standards consistent with the principles underlying this report, and

b) private sponsors and researchers involved in such research should voluntarily comply with these safeguards and standards.

Professional societies and trade associations dedicated to reproductive medicine and technology play a central role in establishing policy and standards for clinical care, research, and education. We believe that these organizations can and should play a salutary role in ensuring that all stem cell and embryo research conducted in the United States, including that which is privately funded, conforms to the ethical principles underlying this report. Many of these organizations already have developed policy statements, ethics guidelines, or other directives addressing issues in this report, and the Commission has benefited from a careful review of these materials. These organizations are encouraged to review their professional standards to ensure not only that they keep pace with the evolving science of human ES and EG cell research, but also that their members are knowledgeable about and in compliance with them. For those organizations that conduct research in this area but that lack statements or guidelines addressing the topics of this report, we recommend strongly that they develop such statements or guidelines. No single institution or organization, whether in the public or the private sector, can provide all the necessary protections and safeguards.

The Need for Ongoing Review and Assessment

No system of federal oversight and review of such a sensitive and important area of investigation should be established without simultaneously providing an evaluation of its effectiveness, value, and ongoing need. The pace of scientific development in human ES and EG cell research likely will increase. Although one cannot predict the direction of the science of human stem cell research, in order for the American public to realize the promise of this research and to be assured that it is being conducted responsibly, close attention to and monitoring of all the mechanisms established for oversight and review are required.

Recommendation 13: Sunset Provision for National Panel

The National Stem Cell Oversight and Review Panel described in Recommendation 8 should be chartered for a fixed period of time, not to exceed five years. Prior to the expiration of this period, DHHS should commission an independent evaluation of the panel's activities to determine whether it has adequately fulfilled its functions and whether it should be continued.

There are several reasons for allowing the national panel to function for a fixed period of time and for evaluating its activities before continuing. First, some of the hoped-for results will be available from research projects

that are using the two sources we consider to be ethically acceptable for federal funding. Five years is a reasonable period of time to allow some of this information to amass, offering the panel, researchers, members of Congress, and the public sufficient time to determine whether any of the knowledge or potential health benefits are being realized. The growing body of information in the public registry and database described above (particularly if privately funded researchers and sponsors voluntarily participate) will aid these considerations.

Second, within this period the panel may be able to determine whether additional sources of ES cells are necessary in order for important research to continue. Two arguments are evident for supporting research using embryos created specifically for research purposes: one is the concern that not enough embryos remain for this purpose from infertility treatments, and the other is the recognition that some research requires embryos that are generated particularly for research and/or medical purposes. The panel should assess whether additional sources of ES cells that we have judged to be ineligible for federal funding at this time (i.e., embryos created solely for research purposes) are needed.

Third, an opportunity to assess the relationship between local review of protocols using human ES and EG cells and the panel's review of protocols for the derivation of ES cells will be offered. It will, of course, take time for this national oversight and review mechanism to develop experience with the processes of review, certification, and approval described in this report. Fourth, we hope that the panel will contribute to the national dialogue on the ethical issues regarding research involving human embryos. A recurring theme of our deliberations, and in the testimony we heard, was the importance of encouraging this ongoing national conversation.

The criteria for determining whether the panel has adequately fulfilled its functions should be set forth by an independent body established by DHHS. However, it would be reasonable to expect that the evaluation would rely generally on the seven functions described above in Recommendation 8 and that this evaluation would be conducted by a group with expertise in these areas. In addition, some of the following questions might be considered when conducting this evaluation: Is there reason to believe that the private sector is voluntarily submitting descriptions of protocols involving the derivation of human ES cells to the panel for review? Is the panel reviewing projects in a timely manner? Do researchers find that the review process is substantively helpful? Is the public being provided with the assurance that social and ethical issues are being considered?

Summary

Recent developments in human stem cell research have raised hopes that new therapies will become available that will serve to relieve human suffering. These developments also have served to remind society of the deep moral concerns that are related to research involving human embryos and cadaveric fetal tissue. Serious ethical discussion will (and should) continue on these issues. However, in light of public testimony, expert advice, and published writings, we have found substantial agreement among individuals with diverse perspectives that although the human embryo and fetus deserve respect as forms of human life, the scientific and clinical benefits of stem cell research should not be foregone. We were persuaded that carrying out human stem cell research under federal sponsorship is important, but only if it is conducted in an ethically responsible manner. And after extensive deliberation, the Commission believes that acceptable public policy can be forged, in part, on widely shared views. Through this report, we not only offer recommendations regarding federal funding and oversight of stem cell research, but also hope to further stimulate the important public debate about the profound ethical issues regarding this potentially beneficial research.

Chapter One

Introduction

Introduction

Late in 1998, three separate reports brought to the fore the debate over the scientific and clinical prospects as well as the ethical implications of research using human stem cells—those cells from which the different types of cells in a developing organism grow and that generate new cells throughout an organism's life (Van Blerkom 1994). The initial two reports were published by two independent teams of scientists that had accomplished the isolation and culture of human *embryonic stem cells* (hereafter referred to as *ES cells*) and *embryonic germ cells* (hereafter referred to as *EG cells*). The first report described the successful isolation of EG cells in the laboratory of John Gearhart and his colleagues at The Johns Hopkins University. This team derived stem cells from primordial gonadal tissue obtained from cadaveric fetal tissue (Shamblott et al. 1998). The second described the work of James Thomson and his coworkers at the University of Wisconsin, who derived ES cells from the blastocyst (~100 cells) of an early human embryo donated by a couple who had received infertility treatments (Thomson et al. 1998). Finally, an article in the November 12, 1998, edition of the *New York Times* described work funded by Advanced Cell Technology of Worcester, Massachusetts. Although this work has not yet been verified fully or published in a scientific journal, the company claims that its scientists have caused human somatic cells to revert to the primordial state by fusing them with cow eggs to create a hybrid embryo. From this hybrid embryo, a small clump of cells resembling human ES cells appears to have been isolated (Wade 1998).

Human Stem Cells: An Overview

Although many kinds of stem cells exist within the human body, scientists recognize a hierarchy of types. Some stem cells are more committed—or differentiated—than others. At the earliest stage of embryonic development, the cells of the blastomere are identical to each other and are relatively undifferentiated. Each one is individually capable of generating a whole organism, a quality referred to as *totipotency*. In the next stage, ES cells, although they no longer are capable of producing a complete organism, remain undifferentiated and retain the ability to develop into nearly any cell type found in the human body, representing a type of biological plasticity referred to as *pluripotency*. (The terms *totipotency* and *pluripotency* will be discussed again later in this chapter.) At this point, the ES cells branch out into many types; from each differentiated line, all the specialized cells (e.g., heart, muscle, nerve, skin, or blood) that constitute the tissues and organs of the body will develop (Weiss et al. 1996).

The potential versatility of ES and EG cells derived from the early stage embryo or from cadaveric fetal tissue offers unusual scientific and therapeutic promise. Because these cells have the ability to proliferate and renew themselves over the lifetime of the organism, scientists have long recognized the possibility of using such cells to generate a certain number of specialized cells or tissues, which could permit the generation of new cells or tissue as a treatment for injury or for damage done by diseases such as Alzheimer's disease, Parkinson's disease, heart disease, and kidney failure. Furthermore, scientists regard these cells as an important, perhaps essential, medium for understanding the details of

human development and thus for developing life-saving drugs and other therapies. At the same time, the current source of these cells (the early stage embryo or cadaveric fetal tissue) makes them the subject of significant ethical considerations. Thus, the scientific reports of the successful isolation of these versatile cells simultaneously have raised the prospect of the development of new treatments and perhaps cures for debilitating and even fatal illnesses, while also renewing the debate regarding the ethics of research involving human embryos and cadaveric fetal material.

Ethical Issues

Within days of the publication of these reports and the *New York Times* article, President Clinton wrote to the National Bioethics Advisory Commission with two requests: that the Commission consider the implications of the purported cow-human fusion experiment and report back to him and that it "undertake a thorough review of the issues associated with human stem cell research balancing all ethical and medical considerations." On November 20, 1998, we responded to the President's first request by stating that "any attempt to create a child through the fusion of a human cell and a nonhuman egg would raise profound ethical concerns and should not be permitted." (See Appendix C, which includes these letters of request and response.) Our response was based upon the same principles we relied on when preparing our report to the President entitled *Cloning Human Beings* (1997). We noted, however, that insufficient scientific evidence is available at this time to determine whether the fusing of a human cell with the egg of a nonhuman animal would result in a human embryo. In addition, if the resulting hybrid embryo were to be used as a source of ES cells, it is not clear that those cells would be the same in all respects to those obtained from a nonhybrid human embryo.

The reports of the successful isolation and culture of ES and EG cells have added a new dimension to the ongoing controversy regarding the ethics of research involving human embryos and cadaveric fetal material. This controversy arises from sharply differing moral views regarding elective abortion or the use of embryos for research, and it has fueled the national and international debate over the ethical, legal, and medical issues that arise in this arena. This debate represents both a challenge and an opportunity: a challenge because it concerns important and morally contested questions regarding the beginning of life, and an opportunity because it provides another occasion for serious public discussion about important ethical issues. We are hopeful that this report will contribute to a dialogue that will foster increased public understanding of the ethical issues underlying research on ES and EG cells and an appreciation of the complexity of making responsible public policy in the face of moral disagreement and in light of a realistic appraisal of the scientific and clinical promise of that research.

We believe that most Americans agree that human embryos should be respected as a form of human life, but that disagreement exists both about the form that such respect should take and about what level of protection is owed at different stages of embryonic development. Therefore, embryo research, the purpose of which is not therapeutic to the embryo itself, is bound to raise serious concerns for some about how to resolve the tensions between the ethical imperative to cure diseases and the moral obligation to protect human life. For those who believe that the embryo has the moral status of a person from the moment of conception, research (or any other activity) that would destroy it is considered wrong and should not take place. For others, arriving at an ethically acceptable policy involves a complex balancing of a number of important ethical concerns. Although this is a controversial area, we should not lose sight of a broad area of consensus on which public policy could—in part—be constructed.

In order to respond effectively and responsibly to the President's request to consider issues related to human stem cell research and to "balance all medical and ethical considerations," we determined that it also is necessary to consider certain aspects of the broader issues regarding research using embryonic and/or fetal material. One reason for this approach is that the nature of some of the ethical issues involved depends on the source of the stem cells. For example, ES cells can be derived from early embryos that are destroyed in the process of ES cell

derivation, an act that some people find ethically unacceptable. The use of cadaveric fetal tissue to derive EG cell lines is somewhat less controversial because the fetus is deceased prior to the initiation of the research and because a well-developed system of public oversight for such research is already in place. In addition, the recent demonstration of nuclear transfer techniques (somatic cell nuclear transfer [SCNT]) suggests that transfer of an adult nucleus into an oocyte might under certain conditions create an embryo. However, the use of this technique to combine an animal oocyte with a human diploid nucleus raises additional issues regarding both the nature of the embryo produced and the ethical issues involved. In addition, each source of material bears a unique set of scientific, ethical, and legal distinctions.

We believed that it was especially important to take a broad view of the status of the human embryo and of fetal tissue in relation to biomedical research, because it is likely that science will uncover additional characteristics of the early *ex utero* human embryo or fetal tissues that will raise additional important and unique therapeutic possibilities, separate from those that derive from ES or EG cells. If these developments occur, all of the same ethical considerations that pertain to embryo research and fetal tissue research in general would arise once again.[1] In fact, the 1994 National Institutes of Health Human Embryo Research Panel designated 13 areas in which embryo research could advance scientific knowledge or could lead to important clinical benefits. Among these areas is "the isolation of pluripotential embryonic stem cell lines for eventual differentiation and clinical use in transplantation and tissue repair."[2]

Recent scientific developments require the updating and review of the important work of U.S. bodies that have met previously to address the role of the ethical complexities of human embryo and fetal tissue research, particularly as they relate to the role of federally funded research. In addition, new policy statements from other countries (such as Canada and the United Kingdom) suggest well-thought-out novel approaches that must be considered carefully. In responding to the President's request, therefore, we elected to take a comprehensive approach that built on the work of these reflective efforts, both in this country and abroad.

In our 1997 report, *Cloning Human Beings*, we addressed a specific aspect of cloning, namely where genetic material would be transferred from the nucleus of a somatic cell of an existing human being to an enucleated human egg with the intention of creating a child. At the time that we were preparing this report, the issues surrounding embryo research were not revisited, although we began our discussions recognizing that any effort in humans to transfer a somatic cell nucleus into an enucleated egg likely involves the creation of an embryo, which has the potential to be transferred to a uterus and developed to term. We recognized that ethical concerns surrounding issues of embryo research recently had received extensive analysis and noted that under current law, the use of SCNT to create an embryo solely for research purposes is prohibited in any project involving federal funds. The President's request—together with new developments concerning human ES and EG cell research using embryos remaining after infertility treatments or fetal tissue following elective abortion—requires that we reconsider the appropriateness of using these sources of cells for research purposes.

In this respect it is important to note that research on human embryos, or the creation of human embryos for research purposes, is not only legal in the United States but proceeds without any public oversight as long as 1) federal funds are not involved, 2) Food and Drug Administration regulations do not apply, and 3) the laws of the state in which the research is to be conducted do not forbid such activity. Consequently, most of the public controversy surrounding such activities in the United States has focused on whether it is appropriate for the federal government to sponsor such research when it has significant scientific merit and substantive clinical promise. This question is also the focus of this report.

Framework for This Report

As noted above, President Clinton directed the Commission to conduct a thorough review of the issues associated with human stem cell research balancing all ethical and medical considerations. This approach—balancing or weighing difficult issues—often is used in public policy discussions and has much to recommend

it, particularly when such balancing involves a serious consideration of different moral points of view, the state of scientific and medical developments, and other factors. As discussed more fully in Chapter 4, some of the issues associated with research on human stem cells—the moral status of the human embryo, for example—are especially sensitive and do not lend themselves easily to balancing. We did not, for example, deem the views of those who consider the fetus to have the moral status of a human person from the moment of conception to be of less (or more) moral weight than the views of those who consider the fetus to lack this moral status. Similarly, we did not come to our conclusions simply by balancing potential medical benefits against the potential harms, because the possibility of social benefits, by itself, is not a sufficient reason for federal support of such controversial research, particularly given the interest in stem cell research in the private sector. Nor did we approach this issue based simply upon an interpretation of the existing legal environment. Instead, we combined, as thoughtfully as we could, a number of different perspectives on and approaches to this topic.

Through ongoing discussion and dialogue—informed by scientists, philosophers, legal and religious scholars, members of the public, and others—we developed our moral perspectives on the appropriateness of federal sponsorship of stem cell research involving the derivation and/or use of ES and EG cells, principally focusing on the ethical and scientific issues. We considered the sources of human EG and ES cells and the relevant moral differences that should be evaluated in determining the acceptability of federal funding for the derivation and/or use of cells from each of these sources. In this regard, we were assisted by a number of commissioned papers each of which addressed different aspects of the problem.[3] We also benefited from the input of a group of religious scholars from diverse faith traditions whose views within and across traditions reflected the diversity found within the public as a whole. We then considered some associated ethical issues including voluntary informed consent, the just distribution of potential benefits from stem cell research, and the commodification and sale of the body and its parts. Finally, we considered how and to what extent a mechanism of national oversight and review would provide the necessary assurance that research, conducted responsibly and with accountability, could go forward while protecting and honoring a number of deeply held values. These shared values include

- securing the safety and efficacy of clinical and/or scientific procedures, especially when fundamental ethical and social issues are involved,
- respecting human life at all stages of development, and
- ensuring the responsible pursuit of medical and scientific knowledge.

Although this report primarily addresses the ethical issues associated with the use of federal funds for research to derive and use ES and EG cells, we recognize that considerable work in both of these areas will be conducted under private sponsorship. Thus, our recommendations also may have implications for those working in the private sector.

Definitions Used in This Report

We recognize the need to define clearly the terms that are central to an understanding of this report. Because certain terms, such as *embryo* and *totipotent*, are not always used consistently, it is important to explain how the Commission uses this terminology.

It is most important that the reader understand how the term embryo is used. The Canadian Royal Commission on New Reproductive Technologies elucidated the confusion surrounding the term well in its 1993 report entitled *Proceed with Care: Final Report of the Royal Commission on New Reproductive Technologies*:

> ...In the language of biologists, before implantation the fertilized egg is termed a 'zygote' rather than an 'embryo.' The term 'embryo' refers to the developing entity after implantation in the uterus until about eight weeks after fertilisation. At the beginning of the ninth week after fertilisation, it is referred to as a 'fetus,' the term used until time of birth. The terms embryo donation, embryo transfer, and embryo research are therefore inaccurate, since these all occur with zygotes, not embryos. Nevertheless, because the terms are still commonly used in the public debate,

we continue to refer to embryo research, embryo donation, and embryo transfer (607).

For the sake of consistency and accuracy, when referring to the details of the developmental stages of an entity, we use the following terminology: 1) the developing organism is a *zygote* during the first week after fertilization, 2) the organism is an *embryo* during the second through eighth weeks of development, and 3) the organism is a *fetus* from the ninth week of development until the time of birth. However, in other contexts, we will continue to use the broad terms *embryo research, embryo donation,* and *embryo transfer* to refer to zygotes, because this is how the public commonly uses them.

Because there are several sources of human stem cells, we decided that each type of stem cell should be named in a way that clarifies its original source. Therefore, as discussed earlier, cells derived from the inner cell mass of a blastocyst—those cells within the conceptus that form the embryo proper—are called *ES cells*, and cells that are derived from primordial germ cells of embryos and fetuses are called *EG cells*. In addition, cells derived from teratocarcinomas—malignant embryonic tumors—are called *embryonal carcinoma cells*, and stem cells found in the adult organism are called *adult stem (AS) cells*.

Two other terms that require explanation—because the scientific community disagrees about their meaning—are *totipotent* and *pluripotent*. Some differentiate between the two terms by defining totipotency as the ability to develop into a complete organism and pluripotency as the ability to develop into all of the various cell types of an organism without the capability of developing into an entire organism. Others define a totipotent cell as any cell that has the potential to differentiate into all cells of a developing organism, but that does not necessarily have the ability to direct the complete development of an entire organism. These scientists would then define a pluripotent cell as any cell that has the ability to differentiate into multiple (more than two) cell types. Rather than engage in this debate, for the sake of clarity, we decided to avoid using this terminology in this report, unless it refers directly to specific work or to the statements of others in which these words were included. Instead, this report uses descriptions of the stage of development and the differentiation potential of cells to make clear to the reader which types of cells are being discussed.

Organization of This Report

This report comes at a time when the Commission has completed deliberations regarding the use of human biological materials in research (1999). In that report, we recognized that in research involving such materials as DNA, hair, and skin biopsies, a number of significant ethical issues must be addressed by Institutional Review Boards, researchers, and others; these include issues of privacy and confidentiality, potential discrimination, and stigmatization. As important as these issues are—and they must be handled satisfactorily in order for research to proceed with appropriate protections for human subjects—research on human stem cells, whether they are obtained from fetal tissue following elective abortions or from tissue obtained from embryos remaining after infertility treatments, requires additional and perhaps even deeper ethical reflection.

The Commission's primary goal for this report was the development of a set of recommendations that would provide guidance on the appropriateness of permitting the federal government to fund human ES and EG cell research and on what sorts of constraints, if any, should be placed on such support. This report first presents a summary of some of the key scientific issues involved in stem cell research (Chapter 2). To place our analysis in context and to understand the implications of any new recommendations regarding the oversight and regulation of research using fetal tissue and embryos, Chapter 3 describes the historical and current status of law and regulation governing the research use of these materials. Chapter 4 explores the various ethical issues surrounding the moral status of the embryo and cadaveric fetal tissue and ethical concerns governing the acceptable use of these materials in research. Finally, Chapter 5 offers our conclusions and recommendations regarding federal sponsorship of research and appropriate oversight activities in these ethically controversial areas.

Notes

1 For example, it has been generally recommended by most governmental and professional bodies that have previously examined this issue that research on the *ex utero* pre-implantation embryo should not be conducted beyond the 14th day following fertilization. At 14 days, the first stages of organized development begin, leading over the next few days to the first appearance of differentiated tissues of the body. The Commission concurs with this time limit on research involving the *ex utero* human embryo.

2 The 1994 National Institutes of Health Human Embryo Research Panel was asked to consider various areas of research involving the *ex utero* pre-implantation human embryo and to provide areas that 1) are acceptable for federal funding, 2) warrant additional review, and 3) are unacceptable for federal support. The panel did not consider research involving *in utero* human embryos, or fetuses, because guidelines for such research already exist in the form of regulations.

3 See Appendix H for a list of the papers that were prepared for the Commission. These papers are available in Volume II of this report.

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Chapter Two

Human Stem Cell Research and the Potential for Clinical Application

Introduction

The stem cell is a unique and essential cell type found in animals. Many kinds of stem cells are found in the human body, with some more differentiated—or committed—to a particular function than others. In other words, when stem cells divide, some of the progeny mature into cells of a specific type (e.g., heart, muscle, blood, or brain cells), while others remain stem cells, ready to repair some of the everyday wear and tear undergone by our bodies. These stem cells are capable of continually reproducing themselves and serve to renew tissue throughout an individual's life. For example, they continually regenerate the lining of the gut, revitalize skin, and produce a whole range of blood cells. Although the term *stem cell* commonly is used to refer to the cells within the adult organism that renew tissue (e.g., hematopoietic stem cells, a type of cell found in the blood), the most fundamental and extraordinary of the stem cells are found in the early stage embryo (Van Blerkom 1994). These *embryonic stem (ES) cells*, unlike the more differentiated *adult stem (AS) cells* or other cell types, retain the special ability to develop into nearly any cell type. *Embryonic germ (EG) cells*, which originate from the primordial reproductive cells of the developing fetus, have properties similar to ES cells.

Because stem cells are able to proliferate and renew themselves over the lifetime of the organism—while at the same time retaining all of their multilineage potential—scientists have long recognized that such cells could be used to generate a large number of specialized cells or tissue through amplification, a possibility that could allow the generation of new cells that would treat injury or disease.[1] In fact, if it were possible to control the differentiation of human ES cells in culture, the resulting cells could be used to repair damage caused by such conditions as heart failure, diabetes, and certain neurodegenerative diseases.

In late 1998, three separate reports brought to the fore not only these scientific and clinical prospects but also the controversies inherent in human stem cell research. The first two reports, published by two independent teams of scientists supported by private funds from Geron Corporation, a biotechnology company located in Menlo Park, California, describe the first successful isolation and culture in the laboratory of human ES and EG cells. One team, led by John Gearhart of The Johns Hopkins University School of Medicine in Baltimore, Maryland, derived human EG cells from primordial gonadal tissue, which was obtained from fetal tissue following elective abortion (Shamblott et al. 1998). The second team, led by James Thomson of the University of Wisconsin, derived human ES cells from the blastocyst stage of early embryos donated by couples who had undergone infertility treatment (Thomson et al. 1998). The ES and EG cells derived by each of these means appear to be similar in structure, function, and potential, although additional research is needed in order to verify this claim (Varmus 1998). Finally, an article in the November 12, 1998, edition of the *New York Times* described work funded by Advanced Cell Technology of Worcester, Massachusetts. Although this work has not yet been verified fully or published in a scientific journal, the company claims that its scientists have caused human somatic cells to revert to the primordial state by fusing them with cow eggs to create a hybrid embryo. From this hybrid embryo, a small clump of cells resembling human ES cells appears to have been isolated (Wade 1998).

The methodologies used by these investigators for deriving human ES and EG cells are based on techniques that have been used in mice since the early 1980s and, more recently, from nonhuman primates and other animals. The isolation and culturing of these cells, however, for the first time open certain avenues of important research and future clinical possibilities. At the most basic level, the isolation of these cells allows scientists to focus on how human ES and EG cells differentiate into specific types of cells, with the goal of identifying the genetic and environmental signals that direct their specialization into specific cell types. Such studies using mouse stem cells are ongoing, but comparable studies with human cells will be required in order to determine whether the signals are the same. This research might, for example, lead to the discovery of new ways to treat a variety of conditions, including degenerative diseases, birth defects, and cancer and would build on investigations conducted over the last decade, in which laboratory animals have been used to determine whether ES cells can be used to re-establish tissue in an adult organism (Corn et al. 1991; Diukman and Golbus 1992; Hall and Watt 1989; Hollands 1991). Through processes scientists are only beginning to understand, these primitive stem cells can be stimulated to specialize so that they become precursors to different cell types, which then may be used to replace tissues such as muscle, skin, nerves, or liver. For example, in mid-1999, scientists used mouse ES cells to successfully generate glial (myelin-producing) cells that when transplanted into a rat model of human myelin disease were able to efficiently myelinate axons in the rat's brain and spinal cord (Brustle et al. 1999).

Stem Cell Types

Scientists often distinguish between different kinds of stem cells depending upon their origin and their potential to differentiate. Cells derived from malignant embryonic tumors, or teratocarcinomas, are called *embryonal carcinoma (EC) cells*; cells derived from the inner cell mass of a blastocyst-stage embryo are ES cells, and cells that are derived from precursors of germ cells from a fetus are EG cells. In addition, stem cells can be found in the adult organism, for example, in bone marrow; they may possibly also be found in skin and intestine. These AS cells serve to replenish tissues in which cells often have limited life spans, such as the skin, intestine, and blood. Although interesting new data suggest that stem cells found in the adult organism are not restricted to producing cells from the tissue in which they reside (Bjornson et al. 1999), it is unlikely that these cells are capable of differentiating into all cell types. In contrast, because human ES and EG cells are believed to be capable of differentiating into all cell types, they are likely to be of clinical use in treating a variety of diseases, especially those for which organ-specific stem cells are difficult to isolate and/or use.

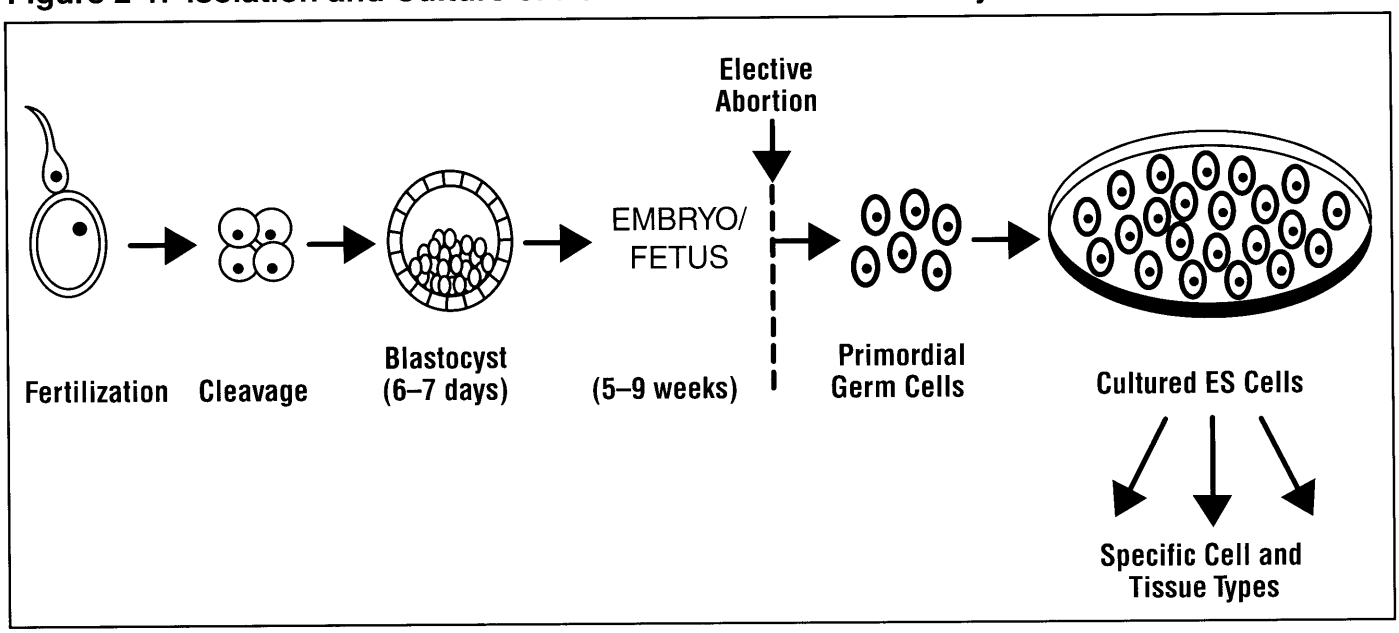
EG Cells

Primordial germ cells are the embryonic precursors of the sperm and ova of the adult animal (Donovan 1998). The establishment of the germline in the embryo involves the separation of primordial germ cells from the somatic cells, the proliferation of primordial germ cells, the migration of these cells to the gonads, and finally their differentiation into gametes (Donovan 1994). Primordial germ cells are the only cells in the body that can give rise to successive generations, while the somatic cells that form the body of the animal lack this capability as soon as they start to differentiate (Matsui 1998).

In culture, primordial germ cells can give rise to EG cells that are capable of differentiating into cells of multiple lineages (Donovan 1998). (See Figure 2-1.) Primordial germ cells normally give rise to gametes, but sometimes if the developmental process goes awry, they become EC cells, the stem cells of benign teratomas and malignant teratocarcinomas, which are tumors containing derivatives of the three primary germ layers (Donovan 1998).

EG cells form embryoid bodies in culture, give rise to teratomas when introduced into histocompatible animals, and form germline chimeras when introduced into a host blastocyst (Donovan 1998). The derivation of EG cells directly from primordial germ cells provides a mechanism to study some aspects of primordial germ cell development, such as imprinting and differentiation (Donovan 1994). At the same time, it may be difficult to obtain an adequate supply of appropriate fetal tissue to

Figure 2-1. Isolation and Culture of Human ES Cells from Embryonic/Fetal Tissue



provide the relevant cell lines needed for both research and clinical uses.

ES Cells

In mammalian embryonic development, cell division gives rise to differentiated daughter cells that eventually comprise the mature animal. As cells become committed to a particular lineage or cell type, a progressive decrease in developmental potential presumably occurs. Early in embryonic development (until about 16 cells), each cell of the early cleavage-stage embryo has the developmental potential to contribute to any embryonic or extra embryonic cell type (Winkel and Pedersen 1988). However, by the blastocyst stage, the cells of the trophectoderm are irreversibly committed to forming the placenta and other trophectoderm lineages (Winkel and Pedersen 1988). By six to seven days postfertilization, the inner cell mass has divided to form two layers, which then give rise to the embryo proper and to extra embryonic tissues (Gardner 1982). (See Exhibit 2-A and Figure 2-2 for a description of early human embryonic development.)

Although the cells of the inner cell mass are precursors to all adult tissues, they can proliferate and replace themselves in the intact embryo only for a limited time before they become committed to specific lineages (Thomson and Marshall 1998). ES cells are derived from cells of the inner cell mass. Once they are placed in the appropriate culture conditions, these cells seem to be capable of extensive, undifferentiated proliferation *in vitro* and maintain the potential to contribute to all adult cell types (Evans and Kaufman 1981; Martin 1981). (See Figure 2-3.)

Even though these embryonic cells are stem cells, they differ substantially from the stem cells found within the fully developed, or adult, organism (see below). Most important, ES cells are highly proliferative, both in the embryo as well as in culture, while some stem cells of the adult can be nearly quiescent and may be more difficult to maintain and expand in culture (Van Blerkom 1994). Therefore, it appears that if stem cells were someday to be used for the treatment of disease, it might be advantageous to use ES cells to treat certain disorders.

Sources of Human ES Cells

We have distinguished between three sources of ES cells, which are derived from early embryos in culture: 1) embryos created by *in vitro* fertilization (IVF) for infertility treatments that were not implanted because they were no longer needed, 2) embryos created by IVF

Exhibit 2-A: Early Development of the Human Embryo

In humans, fertilization (the union of an oocyte [egg] and sperm) occurs in the fallopian tubes and results in the formation of the zygote. In the three to four days it takes for the zygote to travel down the fallopian tube to the uterus, several cell divisions (cleavages) occur.

The first division occurs approximately 36 hours after fertilization, when the zygote begins to cleave into two cells called blastomeres. At about 60 hours following fertilization, the two blastomeres divide again to form four blastomeres. At three days postfertilization, the four blastomeres divide to form eight cells. Each blastomere becomes smaller with each subsequent division. In this early stage of development, all of the blastomeres are of equal size. These cells are unspecialized and have the capacity to differentiate into any of the cell types of the embryo as well as into the essential membranes and tissue that will support the development of the embryo. Therefore, one or more of the blastomeres can be removed without affecting the ability of the other blastomeres to develop into a fetus. In fact, if an embryo separates in half during this early stage of development, identical twins—two genetically identical individuals—will develop.

When the cell division reaches approximately 16 cells, the zygote is called a morula. The morula leaves the fallopian tube and enters the uterine cavity three to four days following fertilization. After reaching the uterus, the developing zygote usually remains in the uterine cavity an additional four to five days before it implants in the endometrium (uterine wall), which means that implantation ordinarily occurs on the seventh or eighth day following fertilization.

Cell division continues, creating a cavity known as a blastocele in the center of the morula. With the appearance of the cavity in the center, the entire structure is now called a blastocyst. This first specialization event occurs just before the zygote attaches to the uterus, approximately six to seven days after fertilization, when approximately 100 cells have developed. This specialization involves the formation of an outer layer of trophoblast cells, which will give rise to part of the placenta, surrounding a group of about 20 to 30 inner cells (the inner cell mass) that remain undifferentiated. At this stage, these cells no longer can give rise to all of the cells necessary to form an entire organism and therefore are incapable of developing into an entire human being. In general, as cells further differentiate, they lose the capacity to enter developmental pathways that were previously open to them.

As the blastocyst attaches to the uterus, the outer layer of cells secretes an enzyme, which erodes the epithelial uterine lining and creates an implantation site for the blastocyst. Once implantation has taken place, the zygote becomes an embryo. The trophoblast and underlying cells proliferate rapidly to form the placenta and the various membranes that surround and nourish the developing embryonic cells.

In the week following implantation, the inner cells of the blastocyst divide rapidly to form the embryonic disc, which will give rise to the three germ layers—the ectoderm, the mesoderm, and the endoderm. These three layers will eventually develop into the embryo. By 14 days, the embryonic disc is approximately 0.5 mm in diameter and consists of approximately 2,000 cells. It is at this time that the first stage of organized development, known as gastrulation, is initiated, leading over the next few days to the first appearance of differentiated tissues of the body, including primitive neural cells. Gastrulation is the process by which the bilaminar (two-layered) embryonic disc is converted into a trilaminar (three-layered) embryonic disc, and its onset at day 14 *in vivo* is marked by the appearance of the primitive streak, a region in which cells move from one layer to another in an organized way.

During the third week, the embryo grows to 2.3 mm long, and the precursors of most of the major organ systems begin to form. At the beginning of the third month, the embryo becomes a fetus. During the third to ninth months, the organ systems and tissues of the fetus continue to develop, until birth.

expressly for research purposes, and 3) embryos resulting from somatic cell nuclear transfer (SCNT) or other cloning techniques. SCNT technology has, in fact, opened the door to a possible alternative approach to creating ES cells. (See Figure 2-4.) If the nucleus is removed from an immature egg (oocyte) and a mature diploid nucleus is inserted, the resulting cell will divide and develop with many characteristics of an embryo. In animal experiments in which a SCNT-derived embryo is transferred to a surrogate mother, a successful pregnancy may be established. (This was the technique used to generate the now-famous cloned sheep Dolly.) If, instead of being transferred to a surrogate, the SCNT-derived embryo is kept in culture, is allowed to divide, and is then dissociated, ES cells can

Figure 2-2. Stages of Development of the Human Embryo and Fetus

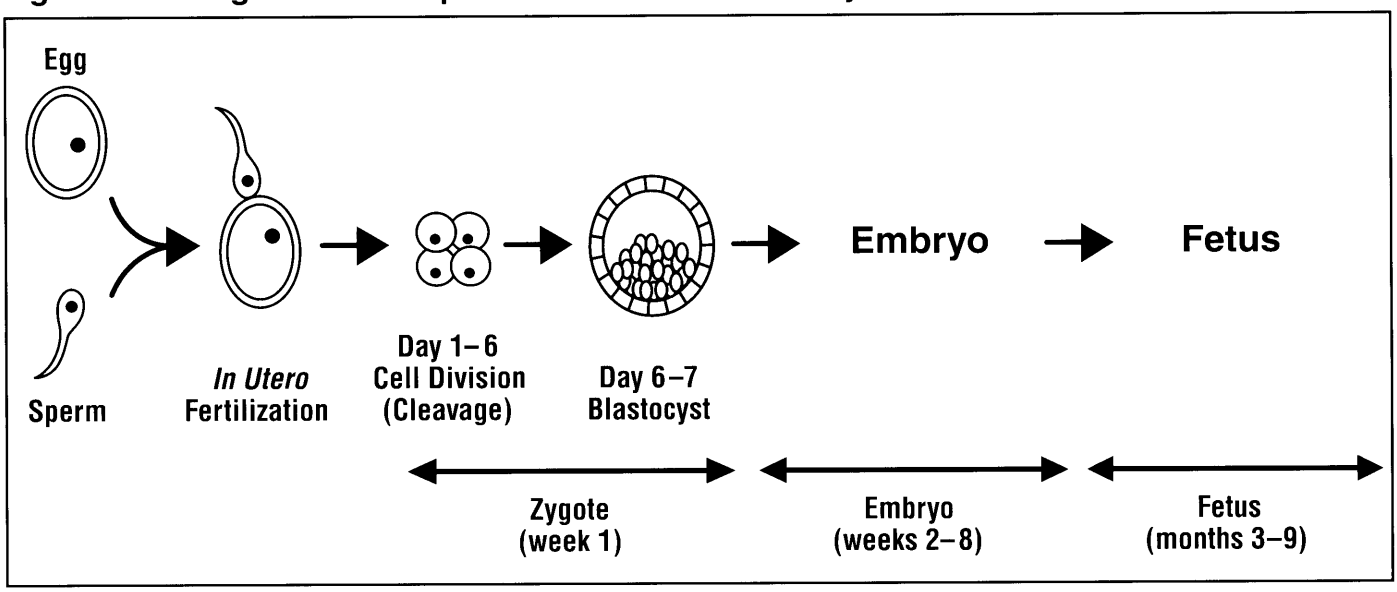
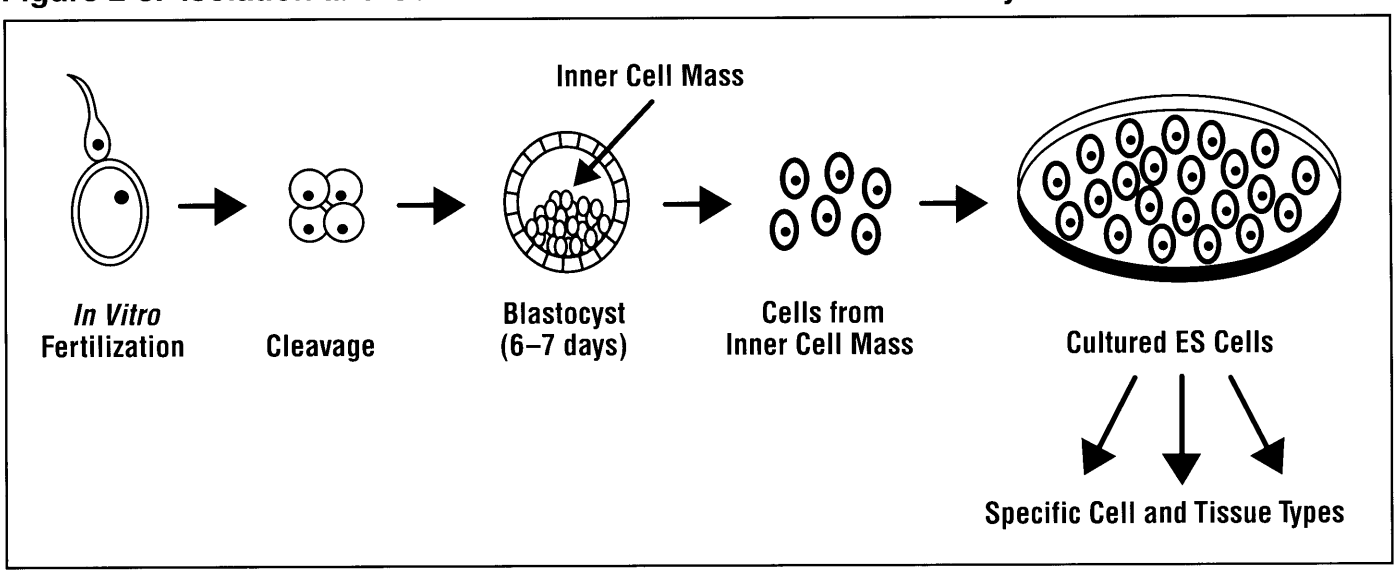


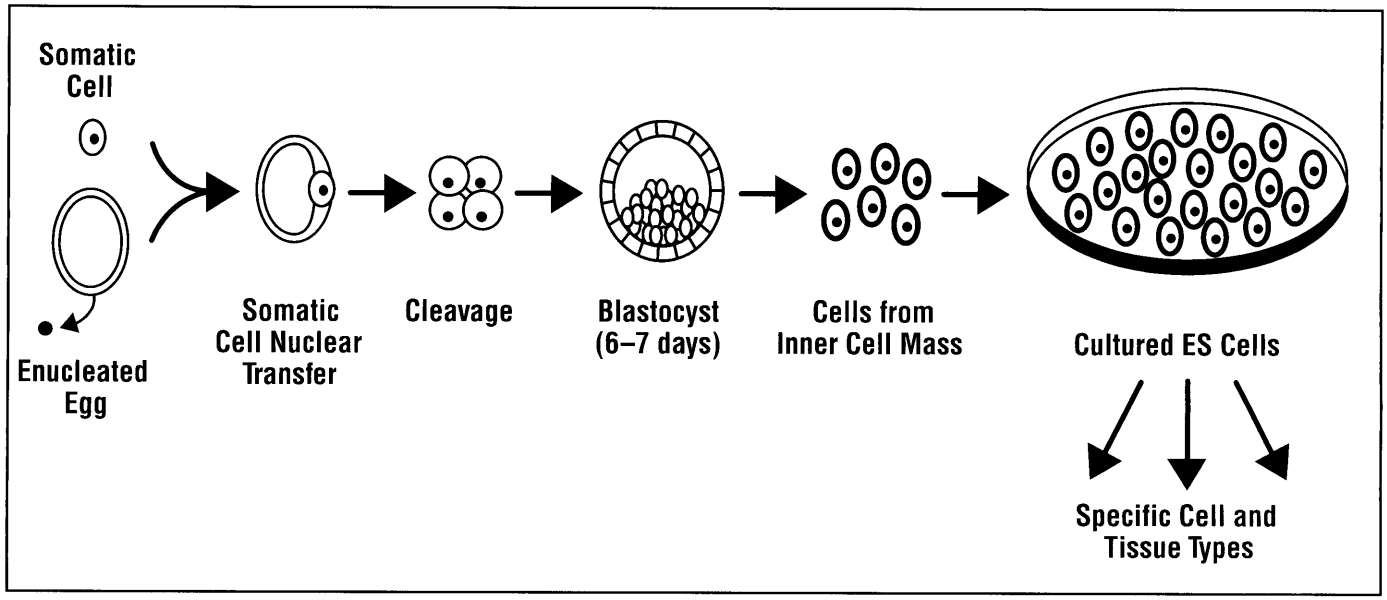
Figure 2-3. Isolation and Culture of Human ES Cells from Blastocysts



be derived. The potential advantage of using SCNT technology to create ES cells is that a somatic cell from an individual can be used to create ES cells that are completely compatible with that individual's tissue type. If cells or tissues are generated from these ES cells for transplant into a person, this tissue type compatibility may avoid many of the problems associated with tissue graft rejection that are currently encountered in the treatment of a variety of diseases.

The use of SCNT into an oocyte has been criticized as an asexual or "unnatural" way of creating a human embryo. However, it is important to distinguish the technique of SCNT from the type of cell that is created; in other words, SCNT techniques also might be used with recipient cells other than oocytes. For example, ES cells with matched tissue types for transplant might be generated by SCNT into an enucleated ES cell.[2] This possibility has not yet been explored, but it may be less morally

Figure 2-4. Isolation and Culture of Human ES Cells from SCNT



problematic to many citizens, because the cell created would not be an embryo with the potential to continue developing.

Stem Cells Found in the Postnatal and Adult Organism

In the adult mammal, cell division occurs in order to maintain a constant number of terminally differentiated cells in tissues in which cells have been lost due to injury, disease, or natural cell death. Cells with a high turnover rate are replaced through a highly regulated process of proliferation, differentiation, and apoptosis (programmed cell death) from relatively undifferentiated stem cells, or precursor cells (Thomson and Marshall 1998). The best known example of an AS cell is the hematopoietic stem cell, which is found in bone marrow and which is responsible for the production of all types of blood cells (Iscove 1990). Other examples of stem cells include the skin epithelium and the epithelium of the small intestine (Hall and Watt 1989). In the human small intestine, for example, approximately 100 billion cells are shed and must be replaced daily (Potten and Loeffler 1990). These tissues contain subpopulations of dividing stem cells that generate replacements for the relatively short-lived, terminally differentiated cells. Much of the debate in the stem cell field revolves around determining the breadth of the potential of these cells: Can they generate only the cells of that organ or are they capable of differentiating into several types of cells when given the proper stimuli?

The successful cloning of Dolly demonstrated that even somatic cells are capable of forming every cell of an organism after nuclear transfer into an oocyte (Wilmut et al. 1997). Preliminary studies of stem cells obtained from various systems of the adult organism suggest that in some cases the reactivation of dormant genetic programs may not require nuclear transfer or experimental modification of the genome. Although research in this area is preliminary, this particular class of stem cells (i.e., AS cells) might be able to differentiate along several cell lineages in response to an appropriate pattern of stimulation.

Neural Stem Cells

For a number of years, scientists have recognized that transplantation of fresh fetal neural tissue into the diseased adult brain may be a promising therapy for neurodegenerative disorders. This type of transplantation recently has been shown to be effective in younger patients with Parkinson's disease (Freed et al. 1999). This technique has several disadvantages, however, such as the need to time the surgery according to the availability of large amounts of fresh fetal tissue, the need to quickly

screen for infectious diseases, and the limited amount of donor fetal tissue available (Bjorklund 1993; Cattaneo and McKay 1991). By developing techniques to culture and expand primary fetal neural cells before transplantation, some of the problems of using fresh tissue may be eliminated. In addition, it might be possible to direct cultured cells to develop along certain lineages or to express specific genes before they are transplanted, so that, for example, dopamine-producing cells could be selectively grown to treat Parkinson's disease (Cattaneo and McKay 1991; Snyder 1994).

Indeed, it has already been demonstrated that neural stem cells are capable of gene (Snyder, Taylor, and Wolfe 1995) and cellular (Rosario et al. 1997; Snyder et al. 1997; Yandava, Billinghurst, and Snyder 1999) replacement in models of neural disease. In many of these experiments, one stable clone of mouse neural stem cells could be used from individual to individual, strain to strain, and disease to disease, regardless of recipient age within the species, without immunorejection or the need for immunosuppression. This suggests that unique immune qualities may exist within stem cells that might allow them to be universal donors. Moreover, the possibility exists that many of the instructive cues for differentiation actually might originate from interaction with damaged central nervous system tissue itself.

The embryonic nervous system arises from the ectoderm. The first cell type to differentiate from the uncommitted precursor cells is the neuron, followed by the oligodendrocyte, and then the astrocyte (Frederiksen and McKay 1988). Recently, Angelo Vescovi, a neurobiologist at the National Neurological Institute Carlo Besta in Milan, Italy, and his colleagues reported that neural stem cells, which give rise to the three main types of brain cells, also can become blood cells when transplanted into mice in which the blood-forming tissue—the bone marrow—has been mostly destroyed (Bjornson et al. 1999). Although the study did not explain what caused the neural cells to turn into blood cells, the investigators speculate that the neural cells might be responding to the same signals that normally stimulate the few remaining blood stem cells to reproduce and mature after irradiation destroys most of the bone marrow (Strauss 1999). Although this research is preliminary and has not yet been conducted using human cells, it raises the possibility of using neural stem cell transplants to treat human blood cell disorders such as aplastic anemia and severe combined immunodeficiency. This is an appealing prospect, because bone marrow stem cells do not replenish themselves well in laboratory cultures. The problem of access to such cells in humans remains, as they must be obtained from the brain—an invasive and risky procedure. This research also opens up the possibility that other apparently restricted AS cells may retain the ability to differentiate into several different types of cells if exposed to a conducive external environment. It is clear that further research is required in this area.

Mesenchymal Stem Cells

Human mesenchymal stem cells, which are present in adult bone marrow, can replicate as undifferentiated cells and have the potential to differentiate into lineages of mesenchymal tissues, including bone, cartilage, fat, tendon, muscle, and marrow stroma (Pittenger et al. 1999). In a recent experiment, cells that have the characteristics of human mesenchymal stem cells were isolated from marrow aspirates of volunteer donors. Individual stem cells were identified that, when expanded to colonies, retained their multilineage potential. These results demonstrate that isolated expanded human mesenchymal stem cells in culture will differentiate, in a controlled manner, to multiple but limited lineages. One might speculate that these particular AS cells could be induced to differentiate exclusively into the adipocytic, chondrocytic, or osteocytic lineages, which then might be used to treat various bone diseases.

The specific environmental cues needed to initiate the proliferation and differentiation of these cells are not understood (Pittenger et al. 1999). The ability to isolate, expand, and direct the differentiation of such cells in culture to particular lineages, however, offers the opportunity to study events associated with cell commitment and differentiation. The human mesenchymal stem cells isolated by Pittenger and colleagues appear to have the ability to proliferate extensively and to maintain the ability to differentiate into certain cell types in culture. Their cultivation and selective differentiation should provide further information about this important progenitor of

multiple tissue types and the potential of new therapeutic approaches for the restoration of damaged or diseased tissue (Pittenger et al. 1999).

Animal Models

ES cells were first derived from mouse embryos, and the mouse has become the principal model for the study of these cells (Evans and Kaufman 1981; Martin 1981). If mouse ES cells are injected into the developing blastocyst, they have the ability to contribute to all three germ layers of the mouse, including the germline, to form a chimeric animal. This is one of the unique properties of the mouse ES cell. More recently, cells with some properties of ES cells have been derived from cows, pigs, rats, sheep, hamsters, rabbits, and primates (Pedersen 1994). (See Table 2-1.) However, only in cows, pigs, and rats did these ES cells contribute to a chimeric animal, and in none of these cases was there contribution to the germline by ES cells, one of the most stringent criteria for defining ES cells.

Mouse ES Cells

ES cells were first isolated from mouse blastocysts in 1981 (Evans and Kaufman 1981; Martin 1981). These blastocysts were placed in culture and allowed to attach to the culture dish so that trophoblast cells spread out, while the undifferentiated inner cells (the inner cell mass) continued to grow as a tight but disorganized cluster. Before the inner cell mass developed into the equivalent of the embryonic disc, it was drawn up into a fine pipette, dissociated into single cells, and dispersed into another dish with a rich culture medium. Under these circumstances, the dissociated cells continued to grow rapidly for an extended period.

Mouse ES cells cannot become organized into an embryo by themselves or implant into the uterus if placed there. However, if the cells are injected back into a new blastocyst, they can intermingle with the host inner cell mass to make a chimera and participate in normal development, eventually contributing to all of the tissues of the adult mouse, including nerve, blood, skin, bone, and germ cells (Robertson and Bradley 1986). This

Table 2-1. Stem Cells Isolated from Mammals

Species	References
Mouse	Evans and Kaufman 1981 Martin 1981
Rat	Iannaccone et al. 1994
Hamster	Doetschman, Williams, and Maeda 1988
Mink	Sukoyan et al. 1992 Sukoyan et al. 1993
Rabbit	Moreadith and Graves 1992 Giles et al. 1993 Graves and Moreadith 1993
Sheep	Handyside et al. 1987 Piedrahita, Anderson, and Bondurant 1990 Notarianni et al. 1991
Pig	Piedrahita et al. 1988 Evans et al. 1990 Notarianni et al. 1990 Piedrahita et al. 1990 Hochereau-de Reiviers and Perreau 1993 Talbot et al. 1993 Wheeler 1994 Shim et al. 1997
Cow	Evans et al. 1990 Saito, Strelchenko, and Niemann 1992 Strelchenko and Stice 1994 Cibelli et al. 1998
Common Marmoset	Thomson et al. 1996
Rhesus Monkey	Thomson et al. 1995
Human	Bongso et al. 1994 Shamblott et al. 1998 Thomson et al. 1998

indicates that mouse ES cells have not lost the capacity to give rise to specialized tissues, but they will not do so unless placed in a conducive environment.

The ability of mouse ES cells to enter the germline in chimeras allows the introduction of specific genetic changes into the mouse genome and offers a direct approach to understanding gene function in the intact animal (Rossant, Bernelot-Moens, and Nagy 1993). Using the technique of homologous recombination in which a gene is either modified or disabled ("knocked out"), mouse ES cells that contain specific gene alterations may be derived. These genetically altered cells can then be used to form chimeras with normal embryos, subsequently generating a mouse lacking one specific gene or containing an extra or altered gene.

Mouse ES cells also have been extremely useful as models of the early differentiation events that occur during the development of mammalian embryos (Pedersen 1994), as shown in the following examples:

- When mouse ES cells were allowed to differentiate in culture, beating heart cells formed spontaneously, providing a model for cardiac-specific gene expression and the development of cardiac muscle and blood vessels (Chen and Kosco 1993; Doetschman et al. 1993; Miller-Hance et al. 1993; Muthuchamy et al. 1993; Robbins et al. 1990; Wobus, Wallukat, and Heschler 1991).
- Blood formation will occur spontaneously in ES cell-derived embryoid bodies and can be augmented by modifying the culture conditions (Snodgrass, Schmitt, and Bruyns 1992). Therefore, hematopoietic stem cells have been studied extensively in an effort to determine the conditions for differentiation, survival, and proliferation of blood cells.
- Several studies have highlighted the importance of growth and differentiation factors in the regulation of mammalian development. For example, the maintenance of mouse ES cells in an undifferentiated state was found to require the presence of leukemia inhibitory factor, a differentiation-inhibiting factor (Fry 1992). Other studies have found several growth and differentiation factors to be important in ES cell development and differentiation, including activins, colony-stimulating factor, erythropoietin, basic fibroblast growth factor, insulin-like growth factor 2, interleukins, parathryoid hormone-related peptide, platelet-derived growth factor, steel factor, and transforming growth factor ß (Pedersen 1994).
- In midgestation embryos and the adult mouse, only one parental allele of imprinted genes is expressed. However, studies have suggested that there is limited relaxation of imprinting in ES cells so that both maternal and paternal alleles are expressed (Pedersen 1994).

By understanding the mechanisms responsible for growth and differentiation in embryonic development, it may then be possible to attempt to regulate the differentiation of ES cells along specific pathways. The knowledge gained from these types of studies could someday lead to the effective treatment of certain important human diseases.

Historically, because of its well-defined genetics, short gestational time, ease of cultivation, and large litters, the mouse has been one of the primary models for the study of mammalian embryonic development. However, there are several differences between early mouse development and early human development, including

- the timing of embryonic genome expression (Braude, Bolton, and Moore 1988),
- the formation, structure, and function of the fetal membranes and placenta (Benirschke and Kaufmann 1990; Luckett 1975, 1978), and
- the formation of an egg cylinder (mouse) as opposed to an embryonic disc (human) (Kaufmann 1992; O'Rahilly 1987).

Thus, other animal models as well as new models that would allow the direct study of human embryonic development are crucial in order to comprehend early human development and to understand the growth requirements of human stem cells of specific lineages.

Bovine ES Cells

The first bovine ES-like cells were reported by Saito, Strelchenko, and Niemann in 1992. More recently, transgenic bovine ES-like cells were derived by using nuclear transfer of fetal fibroblasts to enucleated bovine oocytes (Cibelli et al. 1998). This technique involved introducing a marker gene into bovine fibroblasts from a 55-day-old fetus and then fusing the transgenic fibroblasts to enucleated oocytes to produce blastocyst-stage nuclear

transplant embryos (Cibelli et al. 1998). ES-like cells then were derived from these embryos and were used to create chimeric embryos. When reintroduced into pre-implantation embryos, these transgenic ES-like cells differentiated into derivatives from the three EG layers—ectoderm, mesoderm, and endoderm (Cibelli et al. 1998). Bovine ES cells would be useful in agricultural production of transgenic cows and also may have the potential for generating tissues and organs for use in cross-species transplantation (xenotransplantation) in order to treat human diseases.

Primate ES Cells

Primate ES-like cells have been derived from both the rhesus monkey (Thomson et al. 1995) and the common marmoset (Thomson et al. 1996). When allowed to grow, both marmoset and rhesus ES cells spontaneously differentiate into more complex structures, including cardiac muscle, neurons, endoderm, trophoblast, and numerous unidentified cell types (Thomson and Marshall 1998).

Essential characteristics of these primate ES-like cells include 1) derivation from the pre-implantation or peri-implantation embryo, 2) prolonged undifferentiated proliferation, and 3) stable developmental potential to form derivatives of all three EG layers even after prolonged maintenance in culture (Thomson and Marshall 1998). In addition, although mouse ES cells rarely contribute to trophoblast in chimeras (Beddington and Robertson 1989), primate ES cells differentiate into all three germ layers and trophoblast-like cells (Thomson and Marshall 1998). Furthermore, some primate ES cell lines have maintained a normal karyotype through undifferentiated culture for at least two years, sustained a stable developmental potential throughout this culture period, and maintained the potential to form trophoblast *in vitro* (Thomson et al. 1995, 1996).

Although there is some variation between species, nonhuman primate ES cell lines appear to provide a useful *in vitro* model for understanding the differentiation of human tissues (Thomson and Marshall 1998), and primate ES cells provide a powerful model for understanding human development and disease. Furthermore, because of the similarities between human and primate ES cells, primate ES cells provide a model for developing strategies to prevent immune rejection of transplanted cells and for demonstrating the safety and efficacy of ES cell-based therapies (Thomson et al. 1995).

Human Models

Human ES Cell Lines Derived from Blastocysts

The first successful isolation of cells from the human inner cell mass of blastocysts and their culture *in vitro* for at least two series of cell divisions was reported by Bongso and colleagues in 1994. Starting with 21 spare embryos donated by nine patients in an IVF program,[3] this group isolated cells with typical stem cell characteristics from 17 five-day-old blastocysts (approximately 100 cells) (Bongso et al. 1994). These cells were like ES cells. They were small and round with high nuclear to cytoplasmic ratios, they stained positively for alkaline phosphatase (a biochemical marker for stem cells), and they maintained a normal diploid karyotype. However, after the second subculture, the cells differentiated into fibroblasts or died (Bongso et al. 1994).

In later work, Thomson and his colleagues were able to isolate human ES-like cell lines and grow them continuously in culture for at least five to six months. Although these cells have not passed the most stringent test—as have mouse ES cells—to determine whether they can contribute to the germline, we will continue to use the term *ES cell* throughout this report because both scientists and nonscientists alike have widely applied this term to refer to these cells. This renewable tissue culture source of human cells—capable of differentiating into a wide variety of cell types—is believed to have broad applications in basic research and transplantation therapies (Gearhart 1998).

In Thomson's work, human ES cells were isolated from embryos that were originally produced by IVF for clinical reproductive purposes. (See Exhibit 2-B.) Individuals donated the embryos, following an informed consent process. The consent forms and the entire research protocol were reviewed and approved by an appropriately constituted Institutional Review Board (IRB) (Thomson et al. 1998). Thirty-six embryos were cultured for approximately five days. The inner cell mass was isolated from 14 of the 20 blastocysts that developed,

Exhibit 2-B: *In Vitro* Fertilization (IVF)

The procedure of IVF today is widely available in many countries throughout the world, including the United States. Originally developed for the treatment of infertility due to blocked fallopian tubes, IVF has been extended to assist patients with premature depletion of oocytes, recurrent failure of embryos to implant, and low production of functional sperm. More recently, the technique has been used in conjunction with pre-implantation genetic diagnosis to enable fertile couples at risk for transmitting severe or fatal inherited diseases to have healthy children.

Although details of the IVF procedures vary from center to center, the basic approach is to treat oocyte donors over several days with a regimen of hormones designed to stimulate the final maturation of several follicles within the ovary. This is known as hyperstimulation, a procedure that carries the risk of an adverse reaction of less than 1 percent. Following completion of the hormone treatment, mature follicles are detected by sonography and an average of ten are collected by transvaginal aspiration while the patient is sedated. The oocytes are then fertilized by sperm collected from a male donor and cultured in sterile fluid for about two days. When the zygote has reached the four- to eight-cell stage, between three and six zygotes are transferred to the uterus, and the untransferred embryos, if they are developing normally, are usually frozen. Nonviable embryos are discarded. (See also Figure 2-5.) More recently, IVF specialists have begun culturing embryos to the blastocyst stage before transfer to the uterus.

The efficiency of the IVF procedure is relatively low, with approximately 20 percent of fertilized eggs resulting in successful pregnancies, depending on factors such as age of the recipient and the reason for infertility. In comparison, approximately 30 percent of normally conceived human embryos result in successful pregnancies. Embryos that are not transferred can be cryopreserved and stored indefinitely.

Sources:

National Institutes of Health (NIH). Human Embryo Research Panel. 1994. *Report of the Human Embryo Research Panel.* 2 vols. Bethesda, MD: NIH.

New York State Task Force on Life and the Law. 1998. *Assisted Reproductive Technologies: Analysis and Recommendations for Public Policy.* New York: New York State Task Force on Life and the Law.

and five ES cell lines, originating from five separate embryos, were derived (Thomson et al. 1998). The technique used to derive these human ES cells is essentially the same as that used to isolate nonhuman primate ES cell lines (Thomson et al. 1995).

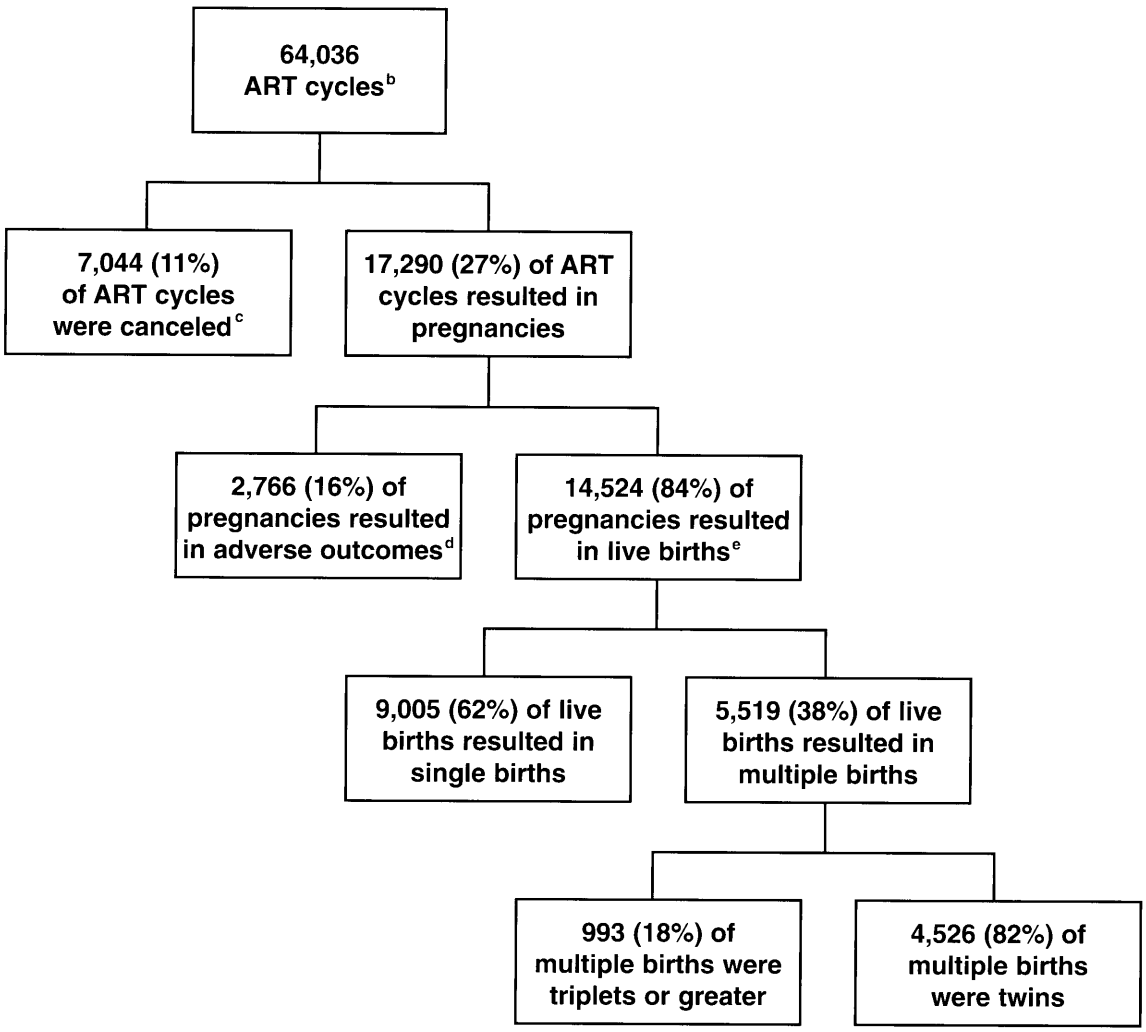
The resulting human ES cell lines had normal karyotypes (two male and three female) and were grown in culture continuously for at least five to six months (Thomson et al. 1998). In addition, the cell lines expressed cell surface markers that also are found on nonhuman primate ES cells (Thomson et al. 1998). Most important, the cell lines maintained the potential to form derivatives of all three EG layers—endoderm, mesoderm, and ectoderm (Thomson et al. 1998).

Many believe that research using human ES cells might offer insights into developmental events that cannot be studied directly in the intact human embryo but that have important consequences in clinical areas such as birth defects, infertility, and miscarriage. Some speculate that the origins of many human diseases (e.g., juvenile-onset diabetes) are due to events that occur early in embryonic development. Such cells also will be particularly valuable for the study of the development and function of tissues that differ between mice and humans. These cells allow for studies that focus on the differentiation of cells into specific tissues and the factors that bring about differentiation, so that cells can be manipulated to generate specific cell types for therapeutic transplantation. Moreover, it may be possible to identify gene targets for new drugs, to manipulate genes that could be used for tissue regeneration therapies, and to understand the teratogenic or toxic effects of certain compounds (Thomson et al. 1998).

Human EG Cells from Fetal Primordial Germ Cells

Primordial germ cells also can give rise to cells with characteristics of ES cells, and, as discussed previously,

Figure 2-5. 1996 Assisted Reproductive Technology (ART) Success Rates[a]



[a] Source: Centers for Disease Control and Prevention (CDC), American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, and RESOLVE. 1998. *1996 Assisted Reproductive Technology Success Rates, National Summary and Fertility Clinic Reports*. Atlanta, GA: CDC.

[b] Data are from 300 U.S. fertility clinics that provided and verified information about the outcomes of all ART cycles started in their clinics in 1996.

[c] Fresh, nondonor cycles were canceled, most commonly because too few (egg) follicles developed. Illness unrelated to the ART procedure also may lead to cancelation. In general, cycles are canceled when chances of success are poor or risks are unacceptably high.

[d] Adverse outcomes included spontaneous abortion (83%), induced abortion (10%), stillbirth (4%), and ectopic pregnancy (3%).

[e] A total of 20,659 babies were born as a result of the 64,036 ART cycles carried out in 1996.

have been designated as EG cells in order to distinguish their tissue of origin (Gearhart 1998). A 1998 report from John D. Gearhart and his colleagues describes the establishment of human EG cell lines from human primordial germ cells (Shamblott et al. 1998). Using an IRB-approved protocol, the human EG cells were isolated from the developing gonads of five- to nine-week-old embryos and fetuses that were obtained following elective abortion (Shamblott et al. 1998). These human EG cell lines have morphological, immunohistochemical, and karyotypic features consistent with those of previously described ES cells and have a demonstrated ability to differentiate *in vitro* into derivatives of the three germ layers (Shamblott et al. 1998).

Fusion of Human Somatic Cells with Cow Eggs to Create Hybrid Embryonic Cells

Advanced Cell Technology of Worcester, Massachusetts, announced in November 1998 that its scientists had made human somatic cells revert to the primordial state by fusing them with cow eggs to create a hybrid embryo (Wade 1998). This work with human cells was performed in 1996 by Jose Cibelli. Using 52 of his own cells—some of them white blood cells and others scraped from the inside of his cheek—Cibelli used a pulse of electricity to fuse each cell with a cow egg from which the nucleus containing the DNA had been removed.[4] Out of these 52 attempts, only one embryo, derived from a cheek epithelial cell, developed into a blastocyst. Approximately 12 days after the fusion of cheek cell and cow egg, sufficient cells existed to allow harvesting of the inner cell mass to produce cells resembling human ES cells. The researchers observed that the hybrid cell quickly became more human-like as the human nucleus took control and displaced bovine proteins with human proteins. However, it is difficult to judge the validity of this work and the nature of the "embryo-like" material produced because the work is extremely preliminary and has not been submitted for peer review or for publication in a scientific journal.

The stated purpose of these experiments was to create an embryo solely for the purpose of establishing an ES cell line that might be used to treat any disease caused by the loss or malfunction of cells, such as Parkinson's disease, diabetes, and heart disease. The researchers emphasized that they had no intention of transferring the resulting hybrid embryos to a uterus, as they considered this to be both unethical and unsafe (Wade 1998).

Growth and Derivation of ES Cells

Human ES cells are different from many adult cells because they have the ability to divide extensively in culture. Although this property has been interpreted by nonscientists as an indication that investigators simply can use existing human ES and EG cell lines (which can be extensively reproduced for a limited time) to study their properties, this is not the case and is a reflection of a misunderstanding of the science that is involved. Evidence from mouse ES cell research suggests that it is essential to derive new ES cell lines repeatedly in order to further our understanding of how to differentiate these cells and grow them extensively in culture.

There are several reasons why it is necessary to repeatedly derive new ES cell lines. First, the properties of ES cells differ depending on the methods used to derive them.[5] Cells derived under some conditions may be limited in their potential to differentiate into a particular tissue type. Second, ES cells are not stable cell types that can simply be mass produced and supplied to an unlimited number of researchers. As these cells grow in culture they accumulate irreversible changes, and the conditions used to grow them can influence the speed at which these changes accumulate. Typically, researchers look only at the ability of ES cells to contribute to some tissues. In one study, however, the ability of ES cells to generate *all* tissue in a mouse was tested (Nagy et al. 1993). This research has shown dramatically that existing cell lines commonly in use by many researchers have lost the ability to generate all mouse tissues and thus to completely generate live mice. When new ES cells were derived and grown for only a short time in culture, they did allow all tissues to be generated. However, after about 14 doublings in culture, even these cells lost their ability to contribute to all tissues. The researchers conclude... "[P]rolonged passage in culture reduces the potential of the ES cell population as a whole. The proportion of cells that retain full potential diminishes with extended

passage" (Nagy et al. 1993). Exactly what changes occur during culture are not yet clear. The chromosome complement remains normal, indicating that this criterion, although frequently used to characterize ES cells, is not a very stringent assay. It could be an accumulation of mutations, changes in gene expression, or epigenetic changes (Nagy et al. 1993). Thus, if one scientist were to obtain cells from a colleague's laboratory, the properties of the cells would depend greatly on the history of how those cells were grown. For this reason, many people who work with mouse ES cells re-derive the cells periodically to be sure the cells have the potential to differentiate into or contribute to many different tissues.

Finally, perhaps the most important reason for deriving new ES cell lines rather than simply working with existing cell lines is that a tremendous amount remains to be learned during the process of derivation itself. It took many laboratories more than ten years to ascertain appropriate conditions for the derivation and growth of mouse ES cells. Research on the growth and derivation of ES cells from other mammalian species is only in its early stages. In fact, only mouse ES cells have the property of contributing to the germline cell lineage—the most stringent criterion for ES cells. Thus, cells from other species are referred to as ES-like cells (Pedersen 1994). Further basic research into the proper conditions to maintain ES cells from many species is ongoing in an attempt to understand the factors necessary to generate stable ES cells. Given that only two successes have been reported on the derivation of human ES and EG cells, it is likely that significant basic research into the appropriate conditions to generate stable stem cells will be needed.

Potential Medical Applications of Human ES Cell and EG Cell Research

Although research into the use of ES and EG cells is still at an early stage, researchers hope to make a contribution to disease treatment in a variety of areas. The ability to elucidate the mechanisms that control cell differentiation is, at the most elemental level, the promise of human ES and EG cell research. This knowledge will facilitate the efficient, directed differentiation of stem cells to specific cell types. The standardized production of large, purified populations of human cells such as cardiomyocytes and neurons, for example, could provide a substantial source of cells for drug discovery and transplantation therapies (Thomson et al. 1998). Many diseases, such as Parkinson's disease and juvenile-onset diabetes mellitus, result from the death or dysfunction of just one or a few cell types, and the replacement of those cells could offer effective treatment and even cures.

Substantial advances in basic cell and developmental biology are required before it will be possible to direct human ES cells to lineages of human clinical importance. However, progress has already been made in the differentiation of mouse ES cells to neurons, hematopoietic cells, and cardiac muscle (Brustle et al. 1997; Deacon et al. 1998; Shamblott et al. 1998). Human ES and EG cells could be put to use in targeting neurodegenerative disorders, diabetes, spinal cord injury, and hematopoietic repopulation, the current treatments for which are either incomplete or create additional complications for those who suffer from them.

Use of Human ES Cells and EG Cells in Transplantation

One of the major causes of organ transplantation and graft failure is immune rejection, and a likely application of human ES and EG cell research is in the area of transplantation. Although much research remains to be done, ES cells derived through SCNT offer the possibility that therapies could be developed from a patient's own cells. In other words, a patient's somatic cells could be fused with an enucleated oocyte and developed to the blastocyst stage, at which point ES cells could be derived for the development of cell-based therapy. This essentially is an autologous transfer. Thus, issues of tissue rejection due to the recognition of foreign proteins by the immune system are avoided entirely. In addition, research to establish xenotransplantation (i.e., interspecies transplantation) as a safe and effective alternative to human organ transplantation is still in its infancy. Alternately, other techniques that would be immunologically compatible for transplantation purposes could be used to generate stem cells, such as

1) banking of multiple cell lines representing a spectrum of major histocompatibility complex (MHC) alleles to serve as a source for MHC matching, and/or

2) creating universal donor lines, in which the MHC genes could be genetically altered so rejection would not occur, an approach that has been tried in the mouse with moderate success (NIAID 1999).

Autologous transplants would obviate the need for immunosuppressive agents in transplantation as it would decrease a central danger to transplant patients—susceptibility to other diseases. Autologous transplants might address problems ranging from the supply of donor organs to the difficulty of finding matches between donors and recipients. Research on ES cells could lead to cures for diseases that require treatment through transplantation, including autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. These cells also might hold promise for treating type-I diabetes (Melton 1999; Varmus 1998), which would involve the transplantation of pancreatic islet cells or beta cells produced from autologous ES cells. These cells would enter the pancreas and provide normal insulin production by replacing the failing resident islet cells.

Studies of Human Reproduction and Developmental Biology

Research using human ES and EG cells could offer insights into developmental events that cannot be studied directly in the intact human embryo but that have important consequences in clinical areas, including birth defects, infertility, and pregnancy loss (Thomson et al. 1998). ES and EG cells provide large quantities of homogeneous material that can be used for biochemical analysis of the patterns of gene expression and the molecular mechanisms of embryonic differentiation.

Cancer Therapy

Human ES and EG cells may be used to reduce the tissue toxicity brought on by cancer therapy (NCI 1999). Already, bone marrow stem cells, representing a more committed stem cell, are used to treat patients after high-dose chemotherapy. However, the recovered blood cells appear limited in their ability to recognize abnormal cells, such as cancer cells. It is possible that injections of ES and EG cells would revive the complete immune response to patients undergoing bone marrow transplantation. Current approaches aimed at manipulating the immune system after high-dose chemotherapy so that it recognizes cancer cells specifically have not yet been successful.

Diseases of the Nervous System

Some believe that in no other area of medicine are the potential benefits of ES and EG cell research greater than in diseases of the nervous system (Gearhart 1998; Varmus 1998). The most obvious reason is that so many of these diseases result from the loss of nerve cells, and mature nerve cells cannot divide to replace those that are lost. For example, in Parkinson's disease, nerve cells that make the chemical dopamine die; in Alzheimer's disease, it is the cells that make acetylcholine that die; in Huntington's disease the cells that make gamma aminobutyric acid die; in multiple sclerosis, cells that make myelin die; and in amyotrophic lateral sclerosis, the motor nerve cells that activate muscles die. In stroke, brain trauma, spinal cord injury, and cerebral palsy and mental retardation, numerous types of cells are lost with no built-in mechanism for replacing them.

Preliminary results from fetal tissue transplantation trials for Parkinson's disease suggest that supplying new cells to a structure as intricate as the brain can slow or stop disease progression (Freed et al. 1999). Yet the difficulty of obtaining enough cells of the right type—that is, dopamine-producing nerve cells—limits the application of this therapy. In 1999, scientists developed methods in animal models to isolate dopamine precursor cells from the dopamine-producing region of the brain and coax them to proliferate for several generations in cell culture. When these cells were implanted into the brains of rodents with experimental Parkinson's disease, the animals showed improvements in their movement control (NINDS 1999). Scientists also have learned to instruct a stem cell from even a nondopamine region to make dopamine (Wagner et al. 1999). A large supply of "dopamine-competent" stem cells, such as ES cell lines, could remove the barrier of limited amounts of tissue. (See Exhibit 2-C.)

Another recent development eventually may provide treatments for multiple sclerosis and other diseases that attack the myelin coating of nerves. Scientists have successfully generated glial cells that produce myelin from

Exhibit 2-C: Potential Treatment for Parkinson's Disease

Parkinson's disease is a degenerative brain disease that affects 2 percent of the population over age 70. Symptoms include slow and stiff movements, problems with balance and walking, and tremor. In more advanced cases, the patient has a fixed, staring expression, walks with a stooped posture and short, shuffling pace, and has difficulty initiating voluntary movements. Falls, difficulty swallowing, incontinence, and dementia may occur in the late stages. Patients often lose the ability to care for themselves and may become bedridden.

The cause of this illness is a deficiency of the neurotransmitter dopamine in specific areas of the brain. Treatment with drugs such as levodopa often is effective in relieving the symptoms. However, as the disease progresses, treatment often becomes more problematic, with irregular responses, difficulty adjusting doses, and the development of side effects such as involuntary writhing movements. Brain surgery with transplantation of human fetal tissue has shown promise as therapy.

Stem cell transplantation also may be a promising therapy for Parkinson's disease. The injection of stem cells that can differentiate into brain cells may offer a means of replenishing neurons that are capable of synthesizing the deficient neurotransmitter. It is possible that stem cell transplantation may be simpler and more readily available than fetal tissue transplantation.

mouse ES cells (Brustle et al. 1999). When these ES cell-derived glial cells were transplanted in a rat model of human myelin disease, they were able to interact with host neurons and efficiently myelinate axons in the rat's brain and spinal cord (Brustle et al. 1999).

Other diseases that might benefit from similar types of approaches include spinal cord injury, epilepsy, stroke, Tay-Sachs disease, and pediatric causes of cerebral palsy and mental retardation. In mice, neural stem cells already have been shown to be effective in replacing cells throughout the brain and in some cases are capable of correcting neurological defects (Lacorazza et al. 1996; Rosario et al. 1997; Snyder et al. 1997; Snyder, Taylor, and Woolfe 1995; Yandava, Billinghurst, and Snyder 1999). Human neural stem cells also have recently been isolated and have been shown to be responsive to developmental signals and to be willing to replace neurons when transplanted into mice (Flax et al. 1998). These recent discoveries of ways to generate specific types of neural cells from ES cells hold much promise for the treatment of severe neurological disorders that today have no known cure.

Diseases of the Bone and Cartilage

Because ES and EG cells constitute a relatively self-renewing population of cells, they can be cultured to generate greater numbers of bone or cartilage cells than could be obtained from a tissue sample. If a self-renewing, but controlled, population of stem cells can be established in a transplant recipient, it could effect long-term correction of many diseases and degenerative conditions in which bone or cartilage cells are deficient in numbers or defective in function. This could be done either by transplanting ES and EG cells to a recipient or by genetically modifying a person's own stem cells and returning them to the marrow. Such approaches hold promise for the treatment of genetic disorders of bone and cartilage, such as osteogenesis imperfecta and the various chondrodysplasias. In a somewhat different potential application, stem cells perhaps could be stimulated in culture to develop into either bone- or cartilage-producing cells. These cells could then be introduced into the damaged areas of joint cartilage in cases of osteoarthritis or into large gaps in bone that can arise from fractures or surgery. This sort of repair would have a number of advantages over the current practice of tissue grafting (NIAMS 1999).

Blood Disorders

The globin proteins are essential for transport of oxygen in the blood, with different globins expressed at different developmental stages. The epsilon globin gene is expressed only in embryonic red blood cells. When this gene—which is not normally expressed in the adult—is artificially turned on in sickle cell patients, it blocks the sickling of the cells that contain sickle cell hemoglobin. Research involving ES cells could help answer questions about how to turn on the epsilon globin gene in adult blood cells and thereby halt the disease process. Stem cell

research also may help produce transplantable cells that would not contain the sickle cell mutation.

Toxicity and Drug Testing

Human stem cell research offers promise for use in testing the beneficial and toxic effects of biologicals, chemicals, and drugs in the most relevant species for clinical validity—humans. Such studies could lead to fewer, less costly, and better designed human clinical trials yielding more specific diagnostic procedures and more effective systemic therapies. Beyond the drug development screening of pharmacological agents for toxicity and/or efficacy, human stem cell research could define new research approaches for clarifying the complex association of environmental agents with human disease processes (NIEHS 1999). It also makes possible a new means of conducting detailed investigations of the underlying mechanisms of the effects of environmental toxins or mixtures of toxins, including their subtle effects on the developing embryonic and fetal development tissue systems.

Transplantable Organs

Several researchers are investigating ways to isolate AS cells and create transplantable organs that may be used to treat a multitude of diseases that do not rely upon the use of embryonic or fetal tissue. Moreover, if it is found to be possible to differentiate ES cells into specific cell types, such stem cells could be an important source of cells for organ growth. For example, recent developments in animals have shown that it may be possible to create entire transplantable organs from a tissue base in a manner that would overcome such problems as the limited supply of organs and tissue rejection. Such a development—producing this tissue base by directing the growth of human embryonic cells—could be a major breakthrough in the field of whole organ transplantation.

For example, using tissue engineering methods, researchers have successfully grown bladders in the laboratory, implanted them into dogs, and shown them to be functional (Oberpenning et al. 1999). To create the bladders, small biopsies of tissue were taken from dog bladders. The biopsied tissue was then teased apart to isolate the urothelial tissue and muscle tissue, which were then grown separately in culture (Tanne 1999). The tissue was then applied to a mold of biodegradable material with the urothelial tissue on the inside and the muscle tissue on the outside. The new organs were transplanted within five weeks (Tanne 1999).

Dogs that received the tissue-engineered organs regained 95 percent of their original bladder capacity, were continent, and voided normally. When the new organs were examined 11 months later, they were completely covered with urothelial and muscle tissue and had both nerve and blood vessel growth. Dogs that did not undergo reconstructive procedures or only received implants of the biodegradable molds did not regain normal bladder function (Oberpenning et al. 1999). This accomplishment marks the first time a mammalian organ has been grown in a laboratory. The ability to create new organs by seeding molds with cells of specific tissue types would be extremely useful in treating children with congenital malformations of organs and people who have lost organs due to trauma or disease (Tanne 1999).

Summary

Currently, human ES cells can be derived from the inner cell mass of a blastocyst (those cells within the conceptus that form the embryo proper), and EG cells can be derived from the primordial germ cells of fetuses. These cells, present in the earliest stages of embryo and fetal development, can generate all of the human cell types and are capable, at least for some time, of self-renewal. A relatively renewable tissue culture source of human cells that can be used to generate a wide variety of cell types would have broad applications in basic research, transplantation, and other important therapies, and a major step in realizing this goal was taken in 1998 with the demonstration that human ES and EG cells can be grown in culture. The clinical potential for these stem cells is vast—they will be important for *in vitro* studies of normal human embryogenesis, human gene discovery, and drug and teratogen testing and as a renewable source of cells for tissue transplantation, cell replacement, and gene therapies.

Notes

1 For a summary of scientific progress in this field see Eiseman, E., "Human Stem Cell Research," RAND DRU-2171-NBAC, September 1999, a background paper prepared for the National Bioethics Advisory Commission.

2 Thomson, J.A., Testimony before NBAC. January 19, 1999. Washington, DC.

3 Consent to carry out this study was approved by the hospital ethical committee based on the guidelines on Assisted Reproductive Technology of the Ministry of Health, Singapore, that experimentation of human embryos up to day 14 of embryonic growth may be allowed (Bongso et al. 1994).

4 The details of this process are described in a European patent application (PCT/U397/12919 1997) and in testimony before the Commission by ACT President Michael West. November 17, 1998. Miami, FL.

5 Hogan, B., Testimony before NBAC. February 3, 1999. Princeton, NJ.

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Chapter Three

The Legal Framework for Federal Support of Research to Obtain and Use Human Stem Cells

Introduction

In the course of attempting to realize the promise of human *embryonic stem (ES) cell* and *embryonic germ (EG) cell* research to advance basic and applied science as well as to develop new, life-saving therapies, biomedical researchers encounter uncertainties in the law as well as explicit restrictions (including bans on federal research funding) that were created in response to earlier developments in biomedical science and public policy. At the same time, provisions also exist in state and federal law designed to facilitate this field of research and to establish—or offer models for establishing—appropriate safeguards to ensure that all efforts to obtain or use stem cells are carried out in an ethically acceptable way. To date, three sources of ES or EG cells—cadaveric fetal tissue, embryos remaining after infertility treatments, and embryos created solely for research purposes using either *in vitro* fertilization (IVF) or, potentially, somatic cell nuclear transfer (SCNT) techniques—have been identified. The goal of this chapter is to examine separately the legal issues raised by research involving each source of EG or ES cells, noting as appropriate when common issues arise.

The Law Relating to Aborted Fetuses as Sources of EG Cells

Federal law permits funding of some research with cells and tissues from the products of elective as well as spontaneous abortions, and state law facilitates the donation and use of fetal tissue for research. Both state and federal law set forth several requirements for the process of retrieving and using material from this source, although amendments may be needed to federal law in order to make existing safeguards applicable to stem cell research.

Federal Law Regarding Research Using Cells and Tissues from Aborted Fetuses

Since as early as the 1930s, American biomedical research has utilized *ex utero* fetal tissue both as a medium and, increasingly, as an object for experimentation (Gelfand and Levin 1993; Zion 1996). "For many years, the production and testing of vaccines, the study of viral reagents, the propagation of human viruses, and the testing of biological products have been dependent on the unique growth properties of fetal tissue" (Duke 1988, D112, D114). For example, the 1954 Nobel Prize for Medicine was awarded to American immunologists who used cell lines obtained from human fetal kidney cells to grow polio virus in cell cultures, a key advance in the development of polio vaccines (Driscoll 1985; Gelfand and Levin 1993).

In 1972, allegations (some of them quite shocking) about experiments with fetuses both *in* and *ex utero* created an air of controversy (fueled by the greater societal debate about elective abortion) over the use of fetal tissue in research.[1] When Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974, it placed the topic of research using the human fetus at the top of the commission's agenda. Within four months of assuming office, the commissioners were mandated to report on the subject, with the proviso that the presentation of their report to the Secretary of the Department of Health, Education, and Welfare (DHEW)—now the Department of Health and Human Services (DHHS)—would lift the moratorium that Congress had imposed on federal

funding of research using live fetuses.[2] On July 25, 1975, the National Commission submitted its conclusions and recommendations, which formed the basis for regulations that the Department issued later that year on research involving fetuses, pregnant women, and human IVF (1975).

General Regulation of Research with Human Beings Including Fetuses

The 1975 provisions remain as elements of the current federal regulations that aim to protect human subjects participating in research conducted with federal funds—rules that also are followed on a voluntary basis by many institutions in the case of research performed without federal support. The core regulations are set forth in the *Federal Policy for the Protection of Human Subjects*, known as the Common Rule, because the same regulatory provisions have been adopted by most federal agencies and departments that conduct or sponsor research in which human subjects are used. The DHHS regulations appear in Volume 45, Part 46 of the *Code of Federal Regulations*—45 CFR 46. The Common Rule makes up Subpart A of the DHHS regulations, and additional protections for special populations of research subjects appear in three further subparts of 45 CFR 46.

The special provisions applicable to fetal material appear in Subpart B, which covers research on "1) the fetus, 2) pregnant women, and 3) human *in vitro* fertilization" and applies to all DHHS "grants and contracts supporting research, development, and related activities" involving those subjects.[3] The regulations primarily address research that could affect living fetuses adversely. They provide for stringent Institutional Review Board (IRB) consideration, which is based upon the results of preliminary studies on animals and nonpregnant women and on assurances that living fetuses will be exposed only to minimal risk except when the research is intended to meet the health needs of the fetus or its mother.[4] Specific restrictions also are imposed on the inclusion of pregnant women in research activities.

Section 46.210 of Subpart B states that the sole explicit requirement for research involving "cells, tissues, or organs excised from a dead fetus" is that such research "shall be conducted only in accordance with any applicable State or local laws regarding such activities."[5] Some analysts have argued that this is the *only* component of Subpart B applicable to research in which cells or tissues from dead abortuses are used in research (Areen 1988). It appears, however, that even prior to the adoption in 1993 of legislation establishing special rules for using fetal tissue for transplantation, National Institutes of Health (NIH) officials had regarded other, general requirements of Subpart B as applicable to research with tissue from dead fetuses.[6] Specifically, these other provisions exclude researchers from any involvement in the decision to terminate a pregnancy or in an assessment of fetal viability and forbid the payment of any inducements to terminate a pregnancy.[7] This dispute over the scope of Subpart B produces one of the points of uncertainty that may need to be resolved either through legislation or official commentary from NIH's Office for Protection from Research Risks (OPRR), if investigators using cadaveric fetal tissue to generate human EG cells are to proceed with confidence and in an ethical fashion.

The Conditions for Federal Support of Fetal Tissue Transplantation

In the 1980s, medical scientists began experimenting with implanting brain tissue from aborted fetuses into patients with Parkinson's disease as well as patients with other neurological disorders. NIH investigators were among those working in this field, and their protocol to use fetal tissue for transplantation was approved by an internal NIH review body. Although the research complied with Subpart B, then-NIH Director James B. Wyngaarden decided to seek approval from Assistant Secretary for Health Robert E. Windom before proceeding.[8] In March 1988, Windom responded by declaring a temporary moratorium on federally funded transplantation research involving fetal tissue from induced abortions. He also asked NIH to establish an advisory body to consider whether such research should be conducted and under what conditions (Windom 1988). The Human Fetal Tissue Transplantation Research Panel—composed of biomedical investigators, lawyers, ethicists, clergy, and politicians—deliberated until the fall of 1988. Panel members then voted 19-2 to recommend continued funding for fetal tissue transplantation research under guidelines designed to ensure the ethical integrity of any experimental procedures (Adams 1988; Duguay 1992;

Silva-Ruiz 1998). In November 1989, after the transition had been made from the Reagan to the Bush administration, DHHS Secretary Louis Sullivan extended the moratorium indefinitely, based upon the position taken by the minority-voting panel members that fetal tissue transplantation research would increase the incidence of elective abortion (Goddard 1996; Robertson 1993).[9] Attempts by Congress to override the Secretary's decision were not enacted or were vetoed by President Bush.[10]

On January 22, 1993, immediately after President Clinton took office, he instructed the incoming Secretary of DHHS to lift the ban on federal funding for human fetal tissue transplantation research.[11] On February 5, 1993, DHHS Secretary Donna Shalala officially rescinded the moratorium, and, in March 1993, NIH published interim guidelines for research involving human fetal tissue transplantation (OPRR 1994). Provisions to legislate these safeguards were promptly proposed in Congress and included in the NIH Revitalization Act of 1993, which President Clinton signed into law on June 10, 1993.[12]

The 1993 act mirrors most prior statutory and regulatory provisions on research involving tissue from dead fetuses.[13] In general, the Revitalization Act states that any tissue from any type or category of abortion may be used for research on transplantation, but only for "therapeutic purposes." Most agree that this means that research on transplantation that has as its goal the treatment of disease is covered by the act, but that basic laboratory research—which only tangentially can be described as having a therapeutic purpose—would not be covered. Under all conditions, the investigator's research scope is not, however, unfettered. First, research activities in this area must be conducted in accordance with applicable state and local law. The investigator also must obtain a written statement from the donor verifying that a) she is donating fetal tissue for therapeutic purposes, b) no restrictions have been placed on who the recipient will be, and c) the donor has not been informed of the identity of the recipient. Further, the attending physician must sign a statement affirming five additional conditions of the abortion, aimed at insulating a woman's decision to abort from her decision to provide tissue for fetal research. Finally, the person principally responsible for the experiment must also affirm his or her own knowledge of the sources of tissue, that others involved in the research are aware of the tissue status, and that the researcher had no part in the abortion decision or its timing.

The statute provides significant criminal penalties for violation of four prohibited acts: 1) purchase or sale of fetal tissue "for valuable consideration" beyond "reasonable payments [for] transportation, implantation, processing, preservation, quality control, or storage...," 2) soliciting or acquiring fetal tissue through the promise that a donor can designate a recipient, 3) soliciting or acquiring fetal tissue through the promise that the recipient will be a relative of the donor, or 4) soliciting or acquiring fetal tissue after providing "valuable consideration" for the costs associated with the abortion itself.[14]

Research of the type conducted by Gearhart and his colleagues at The Johns Hopkins University, in which primordial germ cells were obtained from the gonadal ridge of human fetuses that had been aborted five to nine weeks after fertilization, arguably is not covered by the fetal tissue transplantation provisions of the 1993 NIH Revitalization Act, because these fetal cells are intended to be cultured and used in laboratory experiments, not transplanted. Nevertheless, if such research were federally supported, it could be subject to the requirements of Subpart B of 45 CFR 46—both the general limitations of § 46.206 (separating the investigators from the abortion process and forbidding payments for pregnancy termination) and the special requirements of § 46.210 for activities involving cells and tissues from dead fetuses. Someday, with the advancement of knowledge about cell differentiation and the like, EG cells derived from dead fetuses may be linked more directly or indirectly with transplantation, at which point the 1993 Act would arguably become applicable.[15] In anticipation of that day, and in order to achieve simplicity in the meantime by applying the same rules to all federally supported research with fetal remains, whether or not for transplantation, it would appear desirable to amend the law to clarify that the safeguards of the 1993 Act apply to research in which EG cells are obtained from dead fetuses after a spontaneous or elective abortion.

State Law Regarding Using Aborted Fetuses as Sources of Stem Cells

As recognized by federal statutes and regulations, state law governs the manner in which cells and tissues from dead fetuses become available for research, principally by statutes, regulations, and case law on organ transplantation. The most basic legal provisions lie in the Uniform Anatomical Gift Act (UAGA), which was first proposed in 1968 and rapidly became the most widely adopted uniform statute. While the UAGA is largely consistent with relevant federal statutes and regulations and should facilitate researchers obtaining cadaveric fetal tissue, a number of states have adopted other statutes that limit or prohibit certain types of research with fetal remains.

Laws Facilitating Donation of Fetal Material for EG Cell Research: The UAGA

The UAGA is relevant not only because federal statutes and regulations explicitly condition funding for research with fetal tissue on compliance with state and local laws, but also because the act applies when EG cell research using fetal tissue does not receive federal funding. The original version of the UAGA was approved by all 50 states and the District of Columbia; a 1987 revision has been enacted by 22 states (Zion 1996).[16] The act establishes a system of voluntary donation of "anatomical gifts" for transplantation, education, and research. It was intended to make it easier for people to authorize gifts of their own body (or parts thereof) through a simple "donor card" executed before the occasion arose, as well as to allow donations to be made with the permission of the next-of-kin, following an order established by the statute. The revised UAGA includes "a stillborn infant or fetus" in the definition of "decedents,"[17] for whom parental consent is determinative.[18] The UAGA also provides that "neither the physician or surgeon who attends the donor at death nor the physician or surgeon who determines the time of death" may be involved in the team that will use the organs removed from the decedent.[19] This section, although it may be waived, seems comparable to the separation that the 1993 NIH Revitalization Act and Subpart B of the DHHS regulations required between the research team and any physicians involved in terminating a pregnancy, determining fetal viability, or assisting in the clinical procedure during which fetal tissue is derived for research purposes.[20]

However, federal law restricts the procedures authorized by the UAGA in one area.[21] The UAGA permits donors to designate recipients—including individual patients—of anatomical gifts. The stricter provisions of the NIH Revitalization Act (which prohibits a donor from having knowledge of an individual transplant recipient) could override this state law in the case of federally supported fetal tissue transplantation, but the issue might not arise regarding stem cell research for two reasons. First, such research does not involve transplantation (and hence at this time is not relevant to the NIH Revitalization Act). Second, according to the Revitalization Act, the only recipient who may be designated by the parents of a dead fetus would be a stem cell researcher or research institution.

Laws Restricting Use of Donated Fetal Material for EG Cell Research

At present, 24 states do not have on their books any statutes "specifically addressing research on embryos or fetuses,"[22] and the restrictions in most of the remaining states principally involve embryos remaining after infertility treatments and limitations aimed at discouraging therapeutic abortions. For example, in 12 states, the law applies only to research with fetuses prior or subsequent to an elective abortion.[23] Six states ban research that involves aborted fetuses or their organs, tissues, or remains,[24] which could cause difficulties for researchers using stem cell lines derived from aborted fetuses "if cell lines are considered 'tissue.'"[25] Six other states permit fetal research when the fetus is deceased, but mandate that the donor must provide consent,[26] although none "specifically address[es] the type of information that must be provided to the progenitors before they are asked for consent."[27] In Pennsylvania, investigators using fetal tissue and recipients of the tissue are required to be informed if the tissue was procured as a result of stillbirth, miscarriage, ectopic pregnancy, abortion, or some other means.[28]

In order to diminish the impact that the potential use of a fetus in research might have on the decision to abort, states have enacted many restrictions on payment for

fetal remains. The broadest prohibitions appear as part of state statutes regulating or prohibiting fetal research. Bans on sale vary in their terminology—an "aborted product of conception,"[29] an "aborted unborn child or the remains thereof,"[30] an "aborted fetus or any tissue or organ thereof,"[31] or an "unborn child"[32] —and exist both in states that permit research on a dead fetus with the mother's consent[33] and in those where it is illegal to conduct research upon any aborted product of conception.[34]

The bans on commercialization have a number of interesting twists. Rhode Island outlaws the selling of an embryo or fetus for purposes that violate the statute (such as research on living embryos or fetuses), but apparently allows payment to the mother for allowing a dead fetus to be used in research, because such research is permissible.[35] Minnesota prohibits the sale of living fetuses or nonrenewable organs but explicitly permits "the buying and selling of a cell culture line or lines taken from a [dead fetus]."[36]

The most widely adopted prohibitions on commercialization of fetal remains are those in Sections 10(a) and (b) of the 1987 revision of the UAGA, which prohibit the sale or purchase of any human body parts for any consideration beyond that necessary to pay for expenses incurred in the removal, processing, and transportation of the tissue.[37] On the federal level, what is in essence the same proscription is included both in the 1993 NIH Revitalization Act, which bars the acquisition or transfer of fetal tissue for "valuable consideration" with the same exceptions,[38] and in the National Organ Transplant Act of 1984 (NOTA), which prohibits the sale of any human organ for "valuable consideration for use in human transplantation"[39] if the sale involves interstate commerce.[40] (In 1988, Congress amended NOTA to include fetal organs within the definition of "human organ," in order to foreclose the sale of fetal tissue as well.[41]) Yet both federal statutes could be interpreted to apply only to sales for transplant or therapeutic purposes, not laboratory research. Moreover, the definition of reasonable processing fees in the federal law (and by extension, the UAGA)[42] is arguably too vague, "leav[ing]...room for unscrupulous tissue processors to abuse the law" (Goddard 1996, 394). If special provisions are adopted to govern federal support of research with fetal material to create human EG cell lines, it would seem advisable to ensure that the provisions lay out more clearly what payments may be made to whom and on what basis for fetal cells and tissues.

The state statutes regulating fetal research have been challenged in several court cases. Generally, limitations have been approved as they relate to live fetuses or to the disposal of aborted fetuses.[43] A few cases have dealt with restrictions on research with dead fetuses or fetal remains. In 1978, Louisiana adopted a statute forbidding virtually all experimentation involving a living fetus ("a live child or unborn child") that was not "therapeutic" to that child, a ban it expanded in 1981 to encompass research with aborted fetal tissue as well.[44] Plaintiffs who argued that the prohibition on research burdened their right of privacy challenged the law.[45] Agreeing, the federal district court concluded that the ban on research did not further the state's compelling interest in protecting the health of the woman, nor did the state's interest in the potential life of the unborn continue past the death of the fetus.[46] Finally, the district court addressed the statute's vagueness, noting that it was not possible, *ex utero*, to distinguish between fetal and maternal tissue and the products of spontaneous and induced abortions.[47] On appeal, the Fifth Circuit ignored the district court's analysis entirely, finding instead that the term "experiment" as used in the statute's prohibition against fetal experimentation was unconstitutionally vague.[48]

The Law Relating to Embryos as Sources of ES Cells

Turning to the second source of human ES cells—embryos created through IVF—one finds that in contrast to the regulatory complexity of the federal and state laws governing research using fetal tissue, the legal framework for research using human embryos is relatively straightforward. With the exception of a few state statutes, no viable regulatory system exists to guide or control the practice of human embryo research in the United States.[49] Regarding federally supported scientists, law prohibits such experimentation, while research conducted in the private sector takes place without any federal medical or bioethical oversight specific to the human embryo.[50] The central issue raised by existing law is whether the recent

scientific developments are important enough to justify modifying, in part, the current blanket ban on federal support by creating a limited exception for certain types of human stem cell research.

Federal Law Regarding Research Using Cells and Tissues from Human Embryos

Federal law regarding research using human embryos by investigators employed or funded by the federal government may best be understood by reviewing Subpart B of the DHHS policy on the protection of human subjects and the rider that has been attached for several years to the DHHS appropriation, most recently in the Omnibus Consolidated and Emergency Supplemental Appropriations Act for Fiscal Year 1999 (OCESAA).[51]

The former, which continues to provide a basic framework for research, even though reasons exist to question its applicability, originated in concerns about research on the human fetus, but it also applies to "grants and contracts supporting research, development, and related activities involving...human *in vitro* fertilization."[52] At the time these provisions were first promulgated, IVF was still an experimental technique: The birth in England of Louise Brown, the first so-called test tube baby, did not occur until 1978. Recognizing that NIH scientists and others would wish to pursue research on IVF and the earliest stages of human development, the regulations provided that "no application or proposal involving human *in vitro* fertilization may be funded by the Department [until it] has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint."[53] In 1977, NIH received an application from an academic researcher for support of a study involving IVF. After the application had undergone scientific review within NIH, it was forwarded to the Ethics Advisory Board (EAB) appointed by Joseph Califano, then Secretary of DHEW. At its May 1978 meeting, the EAB agreed to review the research proposal. With the increased public interest that followed the birth of Louise Brown that summer, Secretary Califano asked the EAB to study the broader social, legal, and ethical issues raised by human IVF. On May 4, 1979, in its report to the Secretary, the EAB concluded that federal support for IVF research was "acceptable from an ethical standpoint" provided that certain conditions were met, such as informed consent for the use of gametes, an important scientific goal "not reasonably attainable by other means," and not maintaining an embryo "*in vitro* beyond the stage normally associated with the completion of implantation (14 days after fertilization)" (DHEW EAB 1979, 106, 107). No action was ever taken by the Secretary with respect to the board's report; for other reasons, the Department dissolved the EAB in 1980. Because it failed to appoint another EAB to consider additional research proposals, DHEW effectively forestalled any attempts to support IVF, and no experimentation involving human embryos was ever funded pursuant to the conditions set forth in the May 1979 report or through any further EAB review.

Because the Revitalization Act of 1993 effectively ended the de facto moratorium on IVF and other types of research involving human embryos[54] by nullifying the regulatory provision that mandated EAB review,[55] NIH Director Harold Varmus convened the Human Embryo Research Panel to set forth standards for determining which projects could be funded ethically and which should be considered "unacceptable for federal funding."[56] The panel identified several areas of potential research activity that it considered ethically appropriate for federal support, including studies involving the development of ES cells, though only with embryos resulting from IVF or clinical research that have been donated with the consent of the progenitors. The most controversial aspect of the report was its conclusion that it might be ethical to allow researchers to create human embryos for certain research purposes.[57]

In September 1994, the panel submitted its report to the Advisory Committee to the Director (ACD) of NIH, which formally approved the recommendations and transmitted them to Varmus on December 1, 1994. The following day, pre-empting NIH's response, the President declared that federal funds should not be used to support the creation of human embryos for research purposes and directed that NIH not allocate any resources for such requests.[58] Thereafter, Varmus decided to implement the panel's recommendations not proscribed by the President's directive, concluding that NIH could begin to fund research activities involving "surplus" embryos

(Feiler 1998). Before any funding decisions could be made, however, Congress attached a rider to that year's DHHS appropriations bill that stipulated that none of the funds appropriated could be used to support any activity involving "1) the creation of a human embryo or embryos for research purposes; or 2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero* under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 USC 289g(b))."[59]

When the question arose of whether to provide federal funding for human ES cell research using IVF embryos remaining from infertility treatments, Varmus sought the opinion of Harriet Rabb, DHHS General Counsel, regarding the effect of the prohibition in the current appropriations rider. Rabb reported to Varmus that the OCESAA does not prevent NIH from supporting research that uses ES cells derived from this source because the cells themselves do not meet the statutory, medical, or biological definition of a human embryo (NIH OD 1999).[60]

Having concluded that NIH may fund internal and external research that utilizes but does not create human ES cells, NIH has delayed actual funding until an Ad Hoc Working Group of the ACD develops guidelines for the ethical research in this area.[61] The working group began its deliberations in early 1999 and completed draft guidelines on April 8, 1999, which are still undergoing internal review and public comment.[62]

In addition to these guidelines, ES cell research that was supported by federal funds and directly involved human embryos might arguably be subject to the requirements of both Subpart A (the Common Rule) and Subpart B of 45 CFR 46—that is, the research would be required to meet general and specific substantive requirements, would have to be approved by the IRB of the investigator's institution, and might have to undergo further review at the national level. We use the word "arguably" because OPRR has provided no definitive guidance regarding such an interpretation. Indeed, in response to the Commission's inquiry of May 18, 1999, OPRR acknowledged that "although Subpart B does not apply to research involving a human embryo, per se, it does apply to research that involves the process of *in vitro* fertilization. An embryo formed by a means that does not involve *in vitro* fertilization would not be subject to Subpart B."[63] Because no other guidance is provided, we are left to interpret whether embryos (which are not defined in regulation) are human subjects and therefore protected by Subpart B.

Subpart A, which contains the basic requirements for IRB review, informed consent, privacy protection, and the like, aims to protect a "human subject," defined as "a living individual about whom an investigator...obtains (1) data through intervention or interaction...."[64] This definition creates uncertainties about whether the Common Rule applies to embryo research, the derivation of ES cells, and research involving successor stem cells from embryonic sources that require resolution. This is another point upon which a clearer, more accessible interpretation is needed from OPRR if investigators and IRBs are to proceed with confidence regarding a range of stem cell research activities involving human embryos. Assuming that the DHHS regulations apply, the special requirements of Subpart B also would be applicable, because (as previously described) NIH has long taken the position that human IVF research, which is clearly encompassed in Subpart B, encompasses *any* DHHS-funded research involving human embryos not *in utero*. This would mean not only that another EAB could be impaneled by the Secretary pursuant to 45 CFR § 46.204, but also that special responsibility would fall on investigators and IRBs under 45 CFR § 46.205.[65] In addition, special standards would have to be met under 45 CFR § 46.206, including mandates for prior studies involving animals and ensuring the least possible risk. The newly revised 45 CFR 46, Subpart B (not yet finalized) makes no substantive changes that would affect these requirements.[66]

State Law Regarding Research Using Cells and Tissues from Human Embryos

State legislatures have apparently been more concerned about regulating and restricting research using human fetuses or their remains instead of addressing research involving laboratory manipulation of human gametes and early stage embryos. Nonetheless, although

the statutes usually ignore issues (other than commercialization) specific to IVF (Robertson 1990), some could be construed broadly enough to encompass a range of experimental activities involving IVF, including cryopreservation, pre-implantation screening, gene therapy, twinning, cell line development, and basic research (Coleman 1996). The latter two are of obvious relevance to creating stem cell cultures from embryonic sources.

States that regulate cell line development from human embryos either prohibit the practice entirely or restrict it substantially (Coleman 1996). "All ten states that prohibit embryological research have vaguely worded statutes which could encompass cell line development if the statutes were interpreted broadly...[although] some [activity] could be characterized as non-experimental, thus removing it from the scope of experimentation bans" (Coleman 1996, 1358). Issues inherent in cell line development will include the potential for restrictions on downstream commercialization and uncertainty over the extent to which gamete donors must be informed about the nature of and potential commercial uses of the biological materials they donate (Coleman 1996).

Basic research typically involves precommercial scientific activity designed to explore biological processes or to understand genetic and cellular control mechanisms. As noted previously, 24 states and the District of Columbia do not restrict research involving fetuses or embryos.[67] Of the remaining 26 states that regulate embryo or fetal research in one form or another, basic embryological research is prohibited or restricted in 10 (Feiler 1998). Although the degree of regulation of experimental use of embryos under the New Hampshire statute is unlikely to impair ES cell research in that state,[68] the remaining nine states have legislated more broadly, effectively banning all research involving *in vitro* embryos, with penalties mandated in some states, including civil fines and imprisonment.[69]

The subject of commercialization is a potentially important one, affecting both researchers who must acquire embryos from for-profit IVF clinics or other sources and downstream users who may develop derivative, commercial applications from basic embryological and stem cell research. Currently, five states prohibit payment for IVF embryos for research purposes.[70] Eight additional states prohibit payment for human embryos for any purpose.[71] Five states apply ambiguous restrictions that may or may not prohibit sale of embryos, depending upon interpretation or, in some cases, action by state officials.[72] More troubling, some statutes could be interpreted to prevent payment for ES cell lines derived from human embryos (Coleman 1996), although "it is possible that because a cell line is new tissue produced from the genetic material of, but not originally a part of, the embryo, laws proscribing the sale of embryonic tissue may not apply."[73] In line with NOTA and the 1987 revisions of the UAGA, state statutes on organ transplantation now typically prohibit sale of human organs or parts, but none include language likely to impede research involving human embryos.

The Law Relating to Deriving Stem Cells from Organisms Created Through Cloning

The third potential source of human ES cells would involve the use of cloning—that is, SCNT. One possible use of SCNT would be to derive ES cells themselves, thus avoiding the need for embryos. If such a transfer directly into an enucleated stem cell were to be successful, the therapeutic potential of creating cells and tissues for autologous transplantation might be realized without any of the ethical and regulatory problems associated with the creation of embryos.

At present, however, the method for creating human ES cells through SCNT, which has been announced by one scientific team (although not yet published in a scientific journal), involves inserting a somatic cell nucleus into an enucleated oocyte, which, if it then developed, would become a blastocyst from which ES cells would be derived. This approach creates two problems. First, if the blastocyst were characterized as a human embryo (albeit one created asexually rather than by uniting egg and sperm *in vitro*), then the prohibition on federal funding (as well as the restrictions on embryo research in several states) would come into play. Second, the process of carrying out SCNT using human cells has been outlawed by at least two states and may or may not be eligible for federal funding. On March 4, 1997, shortly after the

initial announcement that the Roslin Institute had succeeded in creating Dolly, the cloned sheep, the Office of the White House Press Secretary released a "Memorandum for the Heads of Executive Departments and Agencies," in which the President stated that

> Federal funds should not be used for cloning of human beings. The current restrictions on the use of Federal funds for research involving human embryos do not fully assure this result. In December 1994, I directed the National Institutes of Health not to fund the creation of human embryos for research purposes. The Congress extended this prohibition in FY 1996 and FY 1997 appropriations bills, barring the Department of Health and Human Services from supporting certain human embryo research. However, these restrictions do not explicitly cover human embryos created for implantation and do not cover all Federal agencies. I want to make it absolutely clear that no Federal funds will be used for human cloning. Therefore, I hereby direct that no Federal funds shall be allocated for cloning of human beings.[74]

On June 9, 1997, the President received NBAC's report entitled *Cloning Human Beings* and announced his acceptance of its recommendations, which included a moratorium on publicly or privately funded research to create a child through SCNT but not on laboratory research using the technique. A number of bills have been introduced in Congress to achieve this result—as have other bills that would enact a broader prohibition—but no federal legislation has been adopted. On February 9, 1998, responding to one of those bills (S. 1601, The Human Cloning Prohibition Act), the Executive Office of the President released a Statement of Administration Policy, which provides in part that

> the Administration supports amendments to S. 1601 that would...permit somatic cell nuclear transfer using human cells for the purpose of developing stem cell (unspecified cells capable of giving rise to specific cells and tissues) technology to prevent and treat serious and life-threatening diseases and other medical conditions, including the treatment of cancer, diabetes, genetic disorders, and spinal cord injuries and for basic research that could lead to such treatments.[75]

This statement does not, however, have the force or effect of a Presidential Directive or Executive Order and does not modify the March 1997 Presidential Directive prohibiting funding for human cloning by federal agencies. The resulting uncertainty must be resolved, taking into account the ethical analysis presented in the next chapter.

Summary

As described in Chapter 2, the development of human ES and EG cell lines represents an important advance in biomedicine that promises not only to expand basic scientific understanding but also to improve health and extend life for millions of patients. Even the greatest supporters of this new field recognize, however, that current methods of deriving EG and ES cells from cadaveric fetal tissue and embryos remaining after infertility treatments raise significant ethical issues. Further ethical analysis, which appears in the next chapter of this report, is needed before conclusions can be reached about the goals and principles that should guide policymaking in this field.

Federal law permits the funding of some research that uses tissue from dead fetuses following spontaneous or elective abortion, provided the researchers follow safeguards that aim to separate the decision to abort from the decision to donate material for research, to ensure appropriate consent, and to avoid commercialization of fetal material. The UAGA, which in every state facilitates the process of donating bodies and organs for research as well as transplantation, treats fetuses like other cadavers; the latest version of the statute imposes special conditions on the donation of fetal remains and reinforces the prohibition in federal law against paying for organ donation. The legal framework identified by these statutes is thus favorable to research in which EG cells would be derived from fetal tissue. Some questions remain, however, about the applicability of some of the statutes—for example, the principal set of federal safeguards appears in a statute dealing with fetal tissue transplantation, and EG cell research does not now, and may never, involve directly the transplantation of tissue or cells from a fetus to a patient. Therefore, to overcome the uncertainties and ensure that ethical safeguards are

understood to be applicable to fetal stem cell research, statutory modification and regulatory clarification are desirable.

Confusion also is caused by restrictions and bans in several states on research use of the products of induced abortions; although these statutes seem aimed principally at research with living fetuses, some have—or may be read to have—broader reach. The common theme of these statutes—as in the law on federally funded research—is to erect a significant barrier between a woman's decision to abort a fetus and the separate question of whether fetal remains will be donated for research. To support that barrier, many states employ consent requirements and prohibit payment for fetal remains, so that such material does not become commercialized and thus inappropriately influence the abortion decision.

The picture is clearer but less favorable to research in the area of embryos remaining after infertility treatments. In addition to restrictions and even outright prohibitions in the law of a number of states, riders to DHHS appropriation statutes in recent years rule out the use of these funds in any process in which human embryos are created for research or are destroyed or subject to a risk of injury. Once it has developed special guidelines to ensure that investigators will safeguard the ethics of the process, NIH will fund suitable research projects using human ES cells derived from IVF embryos, although it will not fund the derivation process itself. This position has been denounced by many members of Congress who supported the ban on federal funding of research with embryos and who believe that however the statutory language may be read, its intent clearly is to prohibit research that depends upon the prohibited acts.

The questions raised by this disagreement go beyond interpretation of the language and intent of the DHHS appropriations rider. First, is the justification for research using human ES cells compelling enough to permit an exception to the ban on federal funding for embryo research? Second, can an exception be crafted in a way that continues to give appropriate weight to the values that underlie the ban in the first place? And third, is the justification for using ES cells strong enough to permit funding of the process of deriving these cells from IVF embryos remaining after infertility treatments? Answers to these questions will require evaluation of the scientific and medical aspects of human ES cell research that are described in Chapter 2 in the context of the ethical considerations that are discussed in Chapter 4.

Notes

1 Proposed guidelines for fetal tissue research were released by NIH and DHEW in 38 *Fed. Reg.* 31,738 (1973) (Gelfand and Levin 1993).

2 See National Research Act, Public Law 93-348, Section 201(a), 88 Stat. 348 (1974).

3 45 CFR § 46.201(a) (1997). "The purpose of this subpart [is] to...assure that [applicable research] conform[s] to appropriate ethical standards and relate[s] to important societal needs" (Ibid. at § 46.202).

4 The portions of Subpart B dealing with research on living fetuses were re-enforced by the Human Research Extension Act of 1985. The act directs that no federally supported research may be conducted on a nonviable living human fetus *ex utero* or on a living human fetus *ex utero* for whom viability has not been determined, unless a) the research or experimentation may enhance the health, well-being, or probability of survival of the fetus itself; or b) will pose no added risk of suffering, injury, or death to the fetus where the research or experimentation is for "the development of important biomedical knowledge which cannot be obtained by other means." In either instance, the degree of risk must be the same for fetuses carried to term as for those intended to be aborted (42 USC § 289g 1998).

5 On May 20, 1998, DHHS released for public comment proposed revisions of Subpart B, most of which relate to research with living fetuses. In these revisions, § 46.210 would become § 46.206, which would retain the requirement that research with material from a dead fetus would have to conform to state law. The revised regulation would add that any living individual who becomes personally identified as a result of research on dead fetal or placental material must be treated as a research subject and accorded the protections of the federal Common Rule.

6 During the period of 1987–92, the NIH Office of Science Policy repeatedly stated that NIH applies Subpart B broadly to a range of fetal research activities. For example, in a 1988 memorandum, NIH Director James B. Wyngaarden informed Assistant Secretary for Health Robert E. Windom that "[a]s you know, the NIH conducts all human fetal tissue research in accordance with Federal Guidelines (45 CFR 46)," and provided a 1987 summary of fetal tissue research at NIH that stated that "NIH-supported human fetal tissue research is conducted in compliance with all Federal... regulations regarding the use of human fetal tissue. These regulations include restrictions on tissue procurement [Subpart B] that are intended to prevent possible ethical abuses" (NIH 1987; Memorandum from James B. Wyngaarden to Robert E. Windom, February 2, 1988).

7 45 CFR §§ 46.206 (a)(3) and 46.206(b)(1997).

8 "Although such approval was not required, the Assistant Secretary was consulted because of the scientific and ethical implications of the study" (Ryan 1991, 687).

9 Letter from Louis Sullivan to William Raub, November 2, 1999.

10 See H.R. 2507, 102d Cong., 1st Sess. (1991) (amending Part G of Title IV of the Public Health Service Act). See also H.R. 5495, 102d Cong., 2nd Sess. (1992) (amending Part G of Title IV of the Public Health Service Act and incorporating the establishment of a federally operated national tissue bank as provided by Exec. Order No. 12,806 [1992]). During this period, in an apparent attempt to find an alternative to fetal tissue derived from elective abortion, the administration established (without success) a tissue bank to collect fetal tissue for research from ectopic pregnancies and miscarriages. Exec. Order No. 12,806, 57 *Fed. Reg.* 21,589 (1992). Because spontaneously aborted tissue may contain viral infections or pathological defects, the use of ectopic and miscarried abortuses is disfavored for transplantation and most other research. In October 1992, a consortium of disease advocacy organizations filed suit against DHHS Secretary Sullivan, alleging that the Hyde Amendment, which bars federal funding for abortions, Departments of Labor, Health, Education, and Welfare Appropriations Act of 1977, Public Law 94-439, did not apply to research on and transplantation of fetal tissue. The plaintiffs argued, moreover, that the fetal tissue transplantation research ban was beyond the Department's statutory authority under the law (Bell 1994).

11 See 58 *Fed. Reg.* 7457 (1993).

12 The administration's policies on fetal tissue transplantation did not entirely quell public controversy or congressional interest (GAO 1997).

13 The policy initiated by President Clinton in 1993 and formalized in the 1993 NIH Revitalization Act is in line with the position taken in many other countries that the use of fetal tissue from elective abortions in therapy for people with conditions such as Parkinson's disease is acceptable. As with U.S. laws and regulations, international guidelines emphasize the need to separate the decision to terminate pregnancy from the decision to donate fetal tissue and the need for informed consent for the donation. See Knowles, L.P., 1999, "International Perspectives on Human Embryo and Fetal Tissue Research." This background paper was prepared for NBAC and is available in Volume II of this report.

14 42 USC § 289g-2(a)-(c) (1997). But see Goddard (1996).

15 DHHS General Counsel Harriet Rabb apparently believes that research of the type conducted by Gearhart is already sufficiently connected to transplantation to be subject to the NIH Revitalization Act, though she does not explain how she reached that conclusion. In a January 15, 1999, memorandum to NIH Director Varmus, Rabb concluded that "[t]o the extent human pluripotent stem cells are considered human fetal tissue by law, they are subject to...the restrictions on fetal tissue transplantation research that is conducted or funded by DHHS, as well as to the federal criminal prohibition on the directed donation of fetal tissue." Rabb examined the definition of "fetal tissue" at 42 USC 289g-1(g) which defines it as "tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth" and observed that "some stem cells, for example those derived from the primordial germ cells of non-living fetuses, would be considered human fetal tissue for purposes of [federal law]." Having concluded that primordial germ cells extracted from nonliving fetuses are a type of fetal tissue, the General Counsel went on, without further explanation, to apply the prohibition on sale of fetal tissue, the firewall restrictions, and the donative limitations stipulated in the NIH Revitalization Act, as well as the requirements of 45 CFR § 46.210.

16 National Conference of Commissioners on Uniform State Laws (NCCUSL), *A Few Facts About the Revised Uniform Anatomical Gift Act*, 1987.

17 Uniform Anatomical Gift Act (UAGA) § 1(3). But see Zion (1996): "UAGA...does not differentiate between a fetus donated from a miscarriage or one given through an elective abortion. Presumably, either type of donation is included, but a certain determination is difficult" (1293).

18 Under § 3 of the UAGA, the first two categories of individuals who may consent to donate are a spouse or adult child of the decedent, which would be irrelevant in the case of a fetus, thus giving priority to the next class, the parents. Usually, permission from any member of a class is adequate, unless a majority of the class objects, though as revised, the "UAGA makes the mother's consent determinative unless the father objects, and...does not provide for notice to the father" (Gelfand and Levin 1993, 679). Gelfand and Levin contrast this UAGA provision with 45 CFR § 46.209(d), which requires the father's consent unless his identity or whereabouts "cannot reasonably be ascertained" or he is "unavailable" to consent; however, these provisions apply only "until it has been ascertained whether or not a fetus *ex utero* is viable," and do not apply to donation of a dead fetus or fetal remains.

19 UAGA § 8(b).

20 See, for example, 45 CFR § 46.206(a)(3) ("Individuals engaged in the activity [of research] will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy"); see also Zion (1996): "These provisions create a 'Chinese Wall' between the individuals effecting the abortion and those conducting fetal tissue research and transplantation....While this language standing alone would likely preclude most undue influence, the UAGA also provides for the waiver of the 'Chinese Wall'....[R]evision may be necessary" (1294).

21 There are also state laws whose restrictions regarding choosing tissue recipients are broader, and may have implications for stem cell research. In Pennsylvania, for example, "No person who consents to the procurement or use of any fetal tissue or organ may designate the recipient of that tissue or organ, nor shall any other person or organization act to fulfill that designation" (18 Pa. Cons. Stat. Ann. § 3216(b)(5)). This law unintentionally would create the

situation where an IVF patient could donate her excess embryo for stem cell research, but she could specify that it be used by a particular medical center. She would have to blindly turn it over, and risk it going to a researcher or entity (such as a for-profit company) that she might not approve of. See Andrews, L.B., 1999, "State Regulation of Embryo Stem Cell Research." This background paper was prepared for NBAC and is available in Volume II of this report.

22 Andrews 1999.

23 See Ariz. Rev. Stat. Ann. § 36-2302(A) (subsequent); Ark. Stat. Ann. § 20-17-802 (subsequent); Cal. Health and Safety Code § 123440 (subsequent); Fla. Stat. Ann. § 390.0111(6) (prior or subsequent); Ind. Code Ann. § 16-34-2-6 (subsequent); Ky. Rev. Stat. § 436.026 (subsequent); Mo. Ann. Stat. § 188.037 (prior or subsequent); Neb. Rev. Stat. § 28-346 (subsequent); Ohio Rev. Code Ann. § 2919.14(A) (subsequent); Okla. Stat. Ann. tit. 63, § 1-735(A) (prior or subsequent); Tenn. Code Ann. § 39-15-208 (subsequent); Wyo. Stat. Ann. § 35-6-115 (subsequent).

24 Ariz. Rev. Stat. Ann. § 36-2302, -2303; Ind. Code Ann. § 1 6.34-2-6; N.D. Cent. Code § 14-02.2-01 to -02; Ohio Rev. Code Ann. § 2919.14; Okla. Stat. Ann. tit. 63, § 1-735; S.D. Codified Laws Ann. § 34-23A-17.

25 Andrews 1999. Similarly, Arizona's statute provides that a "person shall not knowingly use any human fetus or embryo, living or dead, or any parts, organs or fluids of any such fetus or embryo resulting from an induced abortion in any manner" (Ariz. Rev. Stat. § 36-2302(A)).

26 Ark. Stat. Ann. § 20-17-802(2); Mass. Ann. Laws ch. 112 § 12J(a)(II); Mich. Comp. Laws Ann. § 333.2687 (must also comply with state's version of the UAGA, Mich. Comp. Laws Ann. § 333.10101 et seq.); 18 Pa. Cons. Stat. Ann. § 3216(b)(1) (mother's consent valid only after decision to abort has been made; no compensation allowed); R.I. Gen. Laws § 11-54-1(d); Tenn. Code Ann. § 39-15-208(a).

27 Even in the context of research on live fetuses, only New Mexico's statute describes the information that must be provided before consent to research involving a fetus is valid. Under the New Mexico law, a woman who is asked to participate in research must be "fully informed regarding possible impact on the fetus" (Andrews 1999, citing N.M. Stat. Ann. § 24-9A-2(b)).

28 18 Pa. Cons. Stat. Ann. § 3216(b)(4).

29 Ohio Rev. Code Ann. § 2919.14.

30 Okla. Stat. Ann. § 1-735.

31 N.D. Cent. Code § 14-02.2-01(2); Mo. Stat. Ann. § 188.036(5).

32 Tenn. Code Ann. § 39-15-208 (also prohibits sale of an aborted fetus); Utah Code Ann. § 76-7-311.

33 Ark. Stat. Ann. § 20-17-802(c); also a crime to possess such material, § 20-17-802(d).

34 See, for example, Ind. Stat. § 35-46-5-1 (applies both to aborted and stillborn fetuses); Ohio Rev. Code Ann. § 2919.14(A); Okla. Stat. Ann. § 1-735(A).

35 R.I. Geb. Laws § 11-54-1(f).

36 Minn. Stat. Ann. § 145.422(3).

37 Of the 23 states in which organ transplant laws forbid payment, two appear inapplicable to using fetal remains in stem cell research: Arizona's statute defines a decedent to include a stillborn infant but not a fetus (Ariz. Rev. Stat. § 36-849(1)), and Kentucky excludes "fetal parts or...any products of the birth or conception" from its definition of "transplantable organs" that may not be sold (Ky. Rev. Stat. Ann. § 311.165(5)(b)).

38 42 USC § 289g-2(a) (1997).

39 National Organ Transplant Act (NOTA) 42 USC § 274e(a) (1997). "Valuable consideration" is defined at 42 USC § 274e(c)(2) (1997) negatively: "'valuable consideration' does not include the reasonable payments associated with the removal, transportation, implantation, processing, preservation, quality control, and storage of a human organ or the expenses of travel, housing, and lost wages incurred by the donor of a human organ in connection with the donation of the organ." A similar definition (excluding donor costs) is provided in the NIH Revitalization Act at 42 USC § 289g-2(d)(3) (1997).

40 Because the definition of "interstate commerce" in NOTA is based upon the Federal Food, Drug and Cosmetic Act, which defines it as "commerce between any State or Territory and any place outside thereof," 21 USC § 321(b), NOTA's prohibitions extend to purchasing organs abroad for importation into the United States. Most countries explicitly prohibit the commercialization of human fetal tissue. The Canadian Royal Commission on New Reproductive Technologies stated that the noncommercialization of reproduction should be considered a guiding principle. The commission recommended that no for-profit trade be permitted in fetal tissue and that the "prohibition on commercial exchange of fetuses and fetal tissue extend to tissues imported from other countries" (1993). This prohibition was intended to prevent the exploitation of poor women, especially in developing countries, who might be persuaded to begin and end pregnancies for compensation.

41 Organ Transplants Amendment Act of 1988, 42 USC § 274(e)(c)(1) (1997). The amendment was specifically intended to prevent the "sale or exchange for any valuable consideration" of fetal organs and tissue. 134 *Cong. Rec.* S10, 131 (27 July 1988).

42 As enacted in six states, the statutes prohibit the sale of human organs but fail to include a definition of "valuable consideration" that stipulates an exemption for miscellaneous overhead expenses; sixteen states provide such an exemption (Andrews 1999).

43 See for example, *Doe v. Rampton*, 366 F. Supp. 189, 194 (D. Utah 1973) (suggesting in dicta that statute provision prohibiting research on live fetus may not be otherwise unconstitutional), vacated and remanded, 410 U.S. 950 (1973) (directing further consideration in light of *Roe*); *Wolfe v. Schroering*, 388 F. Supp. 631, 638 (W.D. Ky. 1974), aff'd in part, rev'd in part on other grounds, 541 F.2d 523 (6th Cir. 1976) (upholding prohibition on experimentation on a viable fetus due to state's interest in the fetus after viability); *Planned Parenthood Association v. Fitzpatrick*, 401 F. Supp.

554 (E.D. Penn. 1975), aff'd without opin sub nom.; *Franklin v. Fitzpatrick*, 428 U.S. 901 (1976) (affirming legitimate state interest in disposal of fetal remains); *Wynn v. Scott*, 449 F. Supp. 1302, 1322 (N.D. Ill. 1978) (medical researchers have no fundamental rights under the Constitution to perform fetal experiments), aff'd on other grounds sub nom.; *Wynn v. Carey*, 599 F.2d 193 (7th Cir. 1979) (upholding state's rational interest in regulating medicine as to viable fetus); *Leigh v. Olson*, 497 F. Supp. 1340 (D.N.D. 1980) (striking fetal disposal statute as vague where it left "humane disposal" undefined and required mother to determine method of disposal); *Akron v. Akron Center for Reproductive Health, Inc.*, 462 U.S. 416 (1983) (struck down local ordinance that, inter alia, mandated humane and sanitary disposal of fetal remains, finding the provision impermissibly vague because it was unclear whether it mandated a decent burial of the embryo at the earliest stages of formation); *Planned Parenthood Association v. City of Cincinnati*, 822 F.2d 1390, 1391 (6th Cir. 1987) (struck down on other grounds, the court noted in dicta that the wording used by the municipal code regulating disposal of aborted fetal tissue might be precise enough to survive scrutiny); *Planned Parenthood of Minnesota v. Minnesota*, 910 F.2d 479 (8th Cir. 1990) (upholding Minnesota's fetal disposal statute against challenge of vagueness and infringement of privacy).

44 La. Rev. Stat. Ann. § 40:1299.35.13. See Clapp (1988): "The Louisiana statute effectively prohibits any research, experimentation, or even observational study on any embryo, fetus, or aborted fetal tissue. The ban encompasses a range of activities, including studies of the safety of ultrasound and pathological study of fetal tissues removed from a woman for the purpose of monitoring her health. Research on IVF is likewise barred. Since the aborted previable fetus is not living or cannot survive for long, no procedure performed upon it could be considered 'therapeutic,' and therefore use of this tissue is likewise prohibited. If performed on tissues from a miscarriage, such experimentation would be acceptable under the statutory scheme" [footnote omitted] (1076–1077).

45 *Margaret S. v. Treen*, 597 F. Supp. 636 (E.D. La. 1984), aff'd sub nom.; *Margaret S. v. Edwards*, 794 F.2d 994 (5th Cir. 1986). See Clapp (1988): The court "specifically note[d] that reproductive choice was 'not limited to abortion decisions...but extends to both childbirth and contraception.' Prohibiting experimentation on fetal tissues could deny a woman knowledge that would influence her own future pregnancies, as well as prohibit procedures of immediate medical benefit such as pathological examination of tissues. The court also found that the prohibition curtailed the development and use of prediagnostic techniques, including amniocentesis. This result constituted a 'denial of health care' and a 'significant burden' on choice made during the first trimester" [footnote omitted] (1078–1079).

46 *Margaret S. v. Treen*, 597 F. Supp. 636, 674-75 (E.D. La. 1984). See Clapp (1988): "The court further suggested the statute would fail even a rational relation test because it failed to serve its own stated purpose of treating the fetus like a human being, since it treated fetal tissue differently from other human tissue" (1079).

47 *Margaret S. v. Treen*, 597 F. Supp. 636, 675-76 (E.D. La. 1984).

48 *Margaret S. v. Edwards*, 794 F.2d 994, 999 (5th Cir. 1986). "The whole distinction between experimentation and testing, or between research and practice, is...almost meaningless, [such that] 'experiment' is not adequately distinguishable from 'test'...every medical test that is now 'standard' began as an 'experiment.'" But see Clapp (1988): "[T]he court hypothesized that the statute was intended 'to remove some of the incentives for research-minded physicians...to promote abortion' and was therefore 'rationally related to an important state interest.' This language suggests that if the statute had not been vague, the court would have applied less than strict scrutiny to a ban on fetal research. The court also implied, in dicta, that the rationale was based on the 'peculiar nature of abortion and the state's legitimate interest in discouraging' it, relying on *H.L. v. Matheson*, 450 U.S. 398, 411–413 (1981)" (1080). A concurring opinion "criticized the majority for avoiding the real constitutional issue raised—that any statutory ban on experimentation would inevitably limit the kinds of tests available to women and their physicians and thus could not help but infringe on fundamental rights" Ibid. at 999–1002 (Williams, J., concurring) (Clapp 1988, 1080). See also *Jane L. v. Bangerter*, 61 F.3d 1493 (10th Cir. 1995) (striking down as vague Utah's criminal prohibition on fetal research which permitted experimentation aimed at acquiring genetic information about the embryo or fetus).

49 Members of Congress who have opposed stem cell funding maintain that "current law...also specifically covers cells and tissue obtained from embryos," citing as applicable 42 USC § 289g-1(b)(2)(ii) ("no alternation of the timing, method, or procedures used to terminate the pregnancy...made solely for the purposes of obtaining the [fetal] tissue") (Members of the House of Representatives 1999). The apparent basis for this assertion is the definition of "human fetal tissue" at 42 USC § 289g-1(g) ("for purposes of this section, the term 'human fetal tissue' means tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion"). Two elements render the congressional arguments unpersuasive: 1) neither 42 USC § 289g-1 nor 289g-2 is directed at embryo or IVF research; rather, both sections are exclusively centered in a conventional understanding of aborted fetal tissue and the issues arising from fetal tissue research; and 2) biological embryology, IVF, and ES cell research typically include only "live" embryos that are maintained in a living state for research purposes until they are either implanted, disaggregated for living unicellular components, or terminated upon the experiment's completion. A "dead human embryo" would, by definition, comprise a multicellular tissue mass in which all cellular functions associated with life activity had previously ceased (clinical cell death), and would be more in the nature of a stored pathology specimen. The draft guidelines of the NIH Ad Hoc Working Group of the Advisory Committee to the Director support this interpretation (NIH Ad Hoc Working Group 1999, 5).

50 Some private sector biotechnology companies have voluntarily undertaken to self-regulate their research activities using IVF embryos through the use of advisory boards and ethical protocols (Geron Ethics Advisory Board 1998).

51 Public Law No. 105-277, 112 Stat. 2681 (1998).

52 45 CFR § 46.201(a).

53 45 CFR § 46.204(d), nullified by section 121(c) of the NIH Revitalization Act of 1993, Public Law 103-43, June 10, 1993; see 59 *Fed. Reg.* 28276 (June 1, 1994).

54 DHHS has considered human embryo research only under the category of IVF research, as defined in Subpart B ("any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means," 45 CFR § 46.203(g)) and hence it had been subject to the requirement of EAB review prior to funding.

55 The 1993 Act deleted the requirement that IVF research be reviewed by an EAB before it could be funded, but it did not remove the remaining subsections of 45 CFR § 46.204, which prescribe the basic structure and functions of the "one or more Ethical Advisory Boards" that "shall be established by the Secretary" to provide advice as needed on individual applications or "general policies, guidelines, and procedures" covered by Subpart B, including the setting of "class of applications or proposals which: (1) must be submitted to the Board, or (2) need not be submitted to the Board" 45 CFR § 46.204 (a)-(c).

56 59 *Fed. Reg.* 28874, 28875 (June 3, 1994) (notice of meeting); (NIH 1994, vol. 1, ix).

57 "[It] would not be wise to prohibit altogether the fertilization and study of oocytes for research purposes....[H]owever, the embryo merits respect as a developing form of human life and should be used in research only for the most serious and compelling reasons....The Panel believes that the use of oocytes fertilized expressly for research should be allowed only under two conditions. The first condition is when the research by its very nature cannot otherwise be validly conducted. The second condition...is when a compelling case can be made that this is necessary for the validity of a study that is potentially of outstanding scientific and therapeutic value" (NIH 1994, vol. 1, xi–xii).

58 "The Director of the National Institutes of Health has received a recommendation regarding federal funding of research on human embryos. The subject raises profound ethical and moral questions as well as issues concerning the appropriate allocation of federal funds. I appreciate the work of the committees that have considered this complex issue and I understand that advances in *in vitro* fertilization research and other areas could derive from such work. However, I do not believe that federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such research. In order to ensure that advice on complex bioethical issues that affect our society can continue to be developed, we are planning to move forward with the establishment of a National Bioethics Advisory Commission over the next year" (Office of the White House Press Secretary, Statement by the President, December 2, 1994). Although technically superseded in its effect by the congressional appropriations rider governing DHHS, the Directive remains effective throughout other Executive agencies. This has not been formally inscribed as an Executive Order.

59 Public Law No. 104-99, Title I, § 128, 110 Stat. 26, 34 (1996). The rider defines "human embryo" as "any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells." NIH has described the effect of the ban as prohibiting "*in vitro* fertilization of a human egg for research purposes where there is no direct therapeutic intent...as well as...research with embryos resulting from clinical treatment and research on parthenogenesis." The rider has been attached to the subsequent DHHS appropriations, through the current Fiscal Year. See Public Law No. 104-208, Div. A, § 101(e), Title V, § 512, 110 Stat. 3009, 3009-270 (1996); Public Law No. 105-78, Title V, § 513, 111 Stat. 1467, 1517 (1997); Public Law No. 105-277, 112 Stat. 2461 (1998).

60 Memorandum from Harriet Rabb to Harold Varmus, January 15, 1999.

61 "NIH funds (including equipment, facilities, and supplies purchased on currently funded grants) should not be used to conduct research using human pluripotent stem cells derived from human fetal tissue or human embryos until further notice....While the NIH proposes to support research utilizing these human pluripotent stem cells, it will not do so until public consultation has occurred, guidelines are issued, and an oversight committee has ensured that each project is in accord with these guidelines. Research on human stem cells derived from sources other than human embryos or fetal tissue will not be subject to these guidelines and oversight: this research will continue to be funded under existing policies and procedures" (NIH 1999). The NIH Director's caution has not avoided public controversy, however (Members of the House of Representatives 1999; Lanza, Arrow, Axelrod, et al. 1999).

62 "Opening Statement of Co-Chair Ezra C. Davidson, Jr., M.D.," Meeting of the NIH Ad Hoc Working Group of the Advisory Committee to the Director, April 8, 1999 (NIH Ad Hoc Working Group 1999).

63 Letter from Gary B. Ellis, Director of the Office for Protection from Research Risks, to Eric M. Meslin, Executive Director of the National Bioethics Advisory Commission (NBAC), June 3, 1999.

64 45 CFR § 46.102(f).

65 In addition to their other duties, IRBs reviewing research subject to Subpart B must "1) Determine that all aspects of the activity meet the requirements of this subpart; 2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and ii) monitoring the progress of the activity and intervening as necessary through such steps as

visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen); 3) Carry out such other responsibilities as may be assigned by the Secretary" (45 CFR § 46.205(a) (1997)). See also 45 CFR § 46.205(c) (1997) ("Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.").

66 See 45 CFR §§ 46.201-210, Subpart B, "Additional DHHS Protections for Pregnant Women, Human Fetuses, and Newborns Involved as Subjects in Research, and Pertaining to Human *In Vitro* Fertilization," *Fed. Reg.* 27794–27804 (May 20, 1998).

67 "In those states...embryo stem cell research is not banned," but see D.C. Code § 6-2601 (1998) prohibiting sale of any part of human body (even cells), a restriction that may extend to human embryos (Andrews 1999).

68 N.H. Rev. Stat. Ann. § 168-B:15 (limiting the maintenance of *ex utero* pre-implantation embryo in a noncryopreserved state to under 15 days and prohibiting the transfer of research embryo to the uterine cavity).

69 Louisiana broadly prohibits research involving IVF embryos. La. Rev. Stat. Ann. §§ 9:121–122 (West 1991). Eight other states restrict embryo research indirectly, banning all research on "live" embryos or fetuses. Fla. Stat. Ann. § 390.0111(6); Me. Rev. Stat. Ann. tit. 22, § 1593 (West 1992); Mass. Ann. Laws ch. 112, § 12j(a)(I) (Law. Co-op. 1996); Mich. Comp. Laws Ann. §§ 333.2685, 333.2686, 333.2692 (West 1992); Minn. Stat. Ann. § 145.422 Subd. 1,2 (West 1989); N.D. Cent. Code §§ 14-02.2-01, 14-02.2-02 (1991); 18 Pa. Cons. Stat. Ann. § 3216(a) (Supp. 1995); R.I. Gen. Laws § 11-54-1(a)-(c) (1994) (Andrews 1999).

70 Me. Rev. Stat. Ann. tit. 22 § 1593; Mass. Ann. Laws ch. 112 § 12(j)(A)(Iv); Mich. Comp. Laws § 333.2609; N.D. Cent. Code § 14-02.2-02(4); and R.I. Gen. Laws § 11-54-1(f).

71 Fla. Stat. Ann. § 873.05; Georgia Code Ann. § 16-12-160 (A) (Except for Health Services Education); Ill. Stat. Ann. Ch 110½ Para. 308.1; La. Rev. Stat. Ann. § 9:122; Minn. Stat. Ann. § 145.422(3) (Live); 18 Pa. Cons. Stat. Ann. § 3216(b)(3) (forbids payment for the procurement of fetal tissue or organs); Texas Penal Code § 48.02; Utah Code Ann. § 76-7-311. But see Feiler (1998): "Although some state laws prohibit the sale of fertilized embryos, they do nothing to prevent the sale of gametes (sperm and eggs), which can easily be converted into research embryos through deliberate fertilization. Payment for sperm and eggs is widespread among American infertility clinics" [citations omitted] (2455).

72 nn. 66; 75; 76; 80. Tenn. Code Ann. § 39-15-208 (199_) and Utah Code Ann. § 76-7-311 (199_) prohibit sale of an "unborn child"; D.C. Code § 6-2601 (199_) and Va. Code § 32.1-289.1 (199_) prohibit sale of all or a portion of the "human body" (D.C.) or a "natural body part" (Va.); two state statutes prohibit sale of specified organs (not including embryos), but permit state health officials to expand the list under prescribed conditions. N.Y. Public Health Law § 4307 (199_); W. Va. Code § 68.50.610(2) (199_) (Andrews 1999).

73 At least one state "prohibits the sale of living [embryos] or non-renewable organs but does allow 'the buying and selling of a cell culture line or lines taken from a non-living human [embryo],'" ibid., citing Minn. Stat. Ann. § 145.422(3) (Andrews 1999, citing Minn. Stat. Ann. § 145.422(3)).

74 Office of the White House Press Secretary, "Memorandum for the Heads of Executive Departments and Agencies," March 4, 1997.

75 Executive Office of the President of the United States, 1998, *Statement of Administration Policy [on] S.1601 (Human Cloning Prohibition Act)* (Washington, DC: Executive Office of the President).

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Chapter Four

Ethical Issues in Human Stem Cell Research

Ethical Issues Relating to the Sources of Human Embryonic Stem or Embryonic Germ Cells

Research involving human embryonic stem (ES) cells and embryonic germ (EG) cells raises several important ethical issues, principally related to the current sources and/or methods of deriving these cells. If, for example, ES and EG cells could be derived from sources other than human embryos or cadaveric fetal material, fewer ethical concerns would be involved in determining a policy for their use for scientific research or clinical therapies. At present, however, the only methods available to isolate and culture human ES and EG cells involve the use of human embryos or cadaveric fetal tissue. Therefore, careful consideration of the ethical issues involved in the use of these sources is an unavoidable component of the advancement of this type of research.

This chapter first considers the ethical issues arising from research involving the derivation and/or use of ES or EG cells from three potential sources: cadaveric fetal tissue, embryos resulting from and remaining after infertility treatments, and embryos created solely for research purposes either by *in vitro* fertilization (IVF) or somatic cell nuclear transfer (SCNT) techniques. The chapter then reviews separately the specific arguments for and against federal funding of this research. Finally, the chapter discusses relevant ethical issues in federal oversight and review of research involving the derivation and/or use of ES or EG cells.[1]

Research with EG Cells Derived from Cadaveric Fetal Tissue

Many of the ethical questions regarding research involving the use of cadaveric fetal tissue were analyzed in depth by the 1988 National Institutes of Health (NIH) Human Fetal Tissue Transplantation Research Panel. What is new in the present context is that, in the near term at least, the materials derived from this tissue would not be transplanted; rather, gonadal tissue (both male and female) would be used as a source for human EG cells. Initially, these cell lines would be used in basic research to determine their nature, to understand their relationship to human development, and to identify differentiation factors that enable such cells to develop into particular tissue types. Later, such cell lines also might be used for the development of transplantation for particular tissue types. The value of cadaveric fetal tissue already has been demonstrated; a broad variety of research materials and reagents derived from cadaveric fetal tissue currently are used in federally funded research.[2]

The ethical acceptability of deriving EG cells from the tissue of aborted fetuses is, for some, closely connected to the ethical acceptability of abortion. Those who believe that elective abortions are morally acceptable are less likely to identify insurmountable ethical barriers to research that involves the derivation and use of EG cells derived from cadaveric fetal tissue. This group might agree that it is necessary to restrict such research by requiring that the decision to donate fetal tissue be separate from the decision to terminate the pregnancy. The purpose of such a requirement would be to protect the pregnant woman against coercion and exploitation rather than to protect the fetus. In addition, even those who find it acceptable to use cadaveric fetal tissue in research might hold that certain uses of such tissue—for example, uses that treat it as nothing more than any other bodily tissue—should be ruled out as disrespectful.

Those who view elective abortions as morally unjustified often—but not always—oppose the research use of tissue derived from aborted fetuses. They usually have no moral difficulty with the use of tissue from spontaneously aborted fetuses or—if they recognize exceptions to the moral prohibition on abortion—from fetuses in cases that they believe are morally justifiable abortions (e.g., to save the pregnant woman's life). However, in general they do not believe that it is possible to derive and use tissue from what they believe are unjustifiably aborted fetuses without inevitable and unacceptable association with those abortions. This association, they believe, usually taints the actions of all those involved in using these materials or in financing research protocols that rely on such tissue. Nevertheless, some opponents of elective abortions believe that it is still possible to support such research as long as effective safeguards are in place to separate abortion decisions from the procurement and use of fetal tissue in research. For them, when appropriate safeguards are in place, using cadaveric fetal tissue from elective abortions for research is relevantly similar to using nonfetal cadavers donated for scientific and medical purposes.

Association with Abortion

Opponents of the research use of fetal materials obtained from elective abortions dispute the claim that it is possible to separate the moral issues surrounding the abortion from those involved in obtaining and using fetal material. They argue that those who obtain and use fetal material from elective abortion inevitably become associated, in ethically unacceptable ways, with the abortions that are the source of the material.[3] They identify two major types of unacceptable association or cooperation with abortion: 1) causal responsibility for abortions and 2) symbolic association with abortions.

1. Causal Responsibility

Some believe that those who provide cadaveric fetal tissue in research are indirectly, if not directly, responsible for the choice of some women to have an abortion. Direct causal responsibility exists where, in this case, someone's actions directly lead a pregnant woman to have an abortion—for example, the researcher offers financial compensation for cadaveric fetal tissue and this compensation leads the pregnant woman to have an abortion she would not otherwise have had. In part because of concerns about direct causal responsibility, the Human Fetal Tissue Transplantation Research Panel (1988) recommended the following safeguards to separate the pregnant woman's decision to abort from her decision to donate fetal tissue:

- The consent of women for abortions must be obtained prior to requesting or obtaining consent for the donation of fetal tissue.
- Those who seek a woman's consent to donate should not discuss fetal tissue donation prior to her decision to abort, unless she specifically requests such information.
- Women should not be paid for providing fetal tissue.
- A separation must be maintained between abortion clinic personnel and those involved in using fetal tissue.
- There should be a prohibition against any alteration of the timing of or procedures used in an abortion solely for the purpose of obtaining tissue.
- Donors of cadaveric fetal tissue should not be allowed to designate a specific recipient of transplanted tissue.

As noted in Chapter 3, several of these safeguards were later adopted in federal legislation regarding the use of aborted fetal tissue in transplantation research, and they appear to be sufficient to avoid direct causal responsibility for abortions in human EG research as well as in transplantation research.

Those involved in research uses of EG cells derived from fetal tissue could be indirectly responsible for abortions if the perceived potential benefits of the research contributed to an increase in the number of abortions. Opponents of fetal tissue research argue that it is unrealistic to suppose that a woman's decision to abort can be kept separate from considerations of donating fetal tissue, as many women facing the abortion decision are likely to have gained knowledge about fetal tissue research through the media or other sources. The knowledge that having an elective abortion might have benefits for future patients through the donation of fetal tissue for research may tip the balance in favor of going through with an abortion for some women who are ambivalent about it. Some argue that the benefits achieved through the routine use of fetal tissue will further legitimize abortion and result in more permissive societal attitudes and policies concerning elective abortion.

It is impossible to eliminate the possibility completely, however slight it may be, that knowledge of the promise of research on EG cells derived from fetal tissue will play a role in some elective abortion decisions, even if only rarely. However, it is not clear how much moral weight ultimately attaches to this possibility. One might be justified in some instances in asserting that if it were not for the research use of fetal tissue following an abortion, a woman might not have chosen to terminate her pregnancy.

But one could assign this kind of causal responsibility to a number of factors that figure into abortion decisions without making ascriptions of indirect causal responsibility, or what is sometimes called moral complicity. For example, a woman might choose to have an abortion principally because she does not want to slow the advancement of her education and career. She might not have had an abortion in the absence of expectations that encourage women to develop their careers. Yet, we would not think it appropriate to charge those who promote such expectations and/or policies as complicit in her abortion. In both this case and that of research, the opportunity to choose abortion is a consequence of a legitimate social policy. The burden on those seeking to end such policies is to show that the risks of harm—both the probability and the magnitude of harm—resulting from the policies outweigh the expected benefits (Childress 1991). This criterion minimally requires evidence of a high probability of a large number of elective abortions that would not have occurred in the absence of those policies. There is, however, no such evidence at present. If compelling evidence did emerge that elective abortions did, or probably would, increase as a result of the research use of cadaveric fetal tissue, this would require a re-examination of the balance of benefits and harms as well as the safeguards that had been put into place to eliminate the potential for direct causal responsibility and reduce the likelihood of indirect causal responsibility for abortions.

2. Symbolic Association

People can become inappropriately associated with what they believe are wrongful acts for which they are not causally responsible. Particularly problematic for many is an association that appears to symbolize approval of the wrongdoing. For example, James Burtchaell maintains that those involved in research on fetal tissue enter a symbolic alliance with the practice of abortion in producing or deriving benefits from it (1988).

A common response is that persons can benefit from what they might consider immoral acts without tacitly approving of those acts. For example, transplant surgeons and transplant recipients may benefit (the latter more directly than the former) from donated organs from victims of murder or drunken driving but nevertheless condemn those wrongful acts (Robertson 1988; Vawter et al. 1991). A researcher who uses cadaveric fetal material in studies to answer important research questions or to study its potential therapeutic effects or the patient who receives the donated tissue need not sanction the act of abortion any more than the transplant surgeon who uses the organs of a murder victim approves of the homicidal act.

Some opponents of fetal tissue research maintain that it implicates those involved in a kind of wrongdoing that cannot be attributed to the transplant surgeon in the example above. Unlike drunken driving and murder, abortion is an institutionalized practice in which certain categories of human life (the members of which are considered by some to have the same moral status as human adults) are allowed to be killed. In this respect, some opponents of abortion go so far as to suggest that fetal tissue research is more analogous to research that benefits from experiments conducted by Nazi doctors during World War II (Bopp 1994).

But whatever one thinks of comparisons between the victims of Nazi crimes and aborted fetuses—and many are outraged by these comparisons—it is possible to concede the comparisons without concluding that human stem cell research involving cadaveric fetal tissue is morally problematic. Of course, some believe that those who use data derived from Nazi experiments are morally complicit with those crimes. For example, William Seidelman writes:

> By giving value to (Nazi) research we are, by implication, supporting Himmler's philosophy that the subjects' lives were 'useless.' This is to argue that, by accepting data derived from their misery we are, post mortem, deriving utility from otherwise 'useless' life. Science could thus stand accused of giving greater value to knowledge than to human life itself (1988, 232).

But one need not adopt this stance. Instead, one can reasonably believe that a scientist's actions must be understood and judged not by their consequences or uses but rather by several other factors, including the scientist's intentions, the social practices of which his or her actions are a part, and the social context in which those practices are embedded. As philosopher Benjamin Freedman wrote:

> A moral universe such as our own must, I think, rely on the authors of their own actions to be primarily responsible for attaching symbolic significance to those actions...[I]n using the Nazi data, physicians and scientists are acting pursuant to their own moral commitment to aid patients and to advance science in the interest of humankind. The use of data is predicated upon that duty, and it is in seeking to fulfill that duty that the symbolic significance of the action must be found (1992, 151).

It is likewise reasonable to maintain that the symbolic significance of support for research using EG cells derived from aborted fetal tissue lies in the commitment and desire to gain knowledge, promote health, and save lives. This research is allied with a worthy cause, and any taint that might attach from the source of the cells appears to be outweighed by the potential good that the research may yield.

Consent and Donation

In previous debates about the use of fetal tissue in research, questions have been raised about who has the moral authority to donate the material. Some assert that, from an ethical standpoint, a woman who chooses abortion forfeits her rights to determine the disposition of the dead fetus. Burtchaell, for instance, argues that "the decision to abort, made by the mother, is an act of such violent abandonment of the maternal trusteeship that no further exercise of such responsibility is admissible" (1988, 9). By contrast, John Robertson argues that this position mistakenly assumes that the persons disposing of cadaveric remains act only as the guardians or proxies of the deceased. Instead, "a more accurate account of their role is to guard their own feelings and interests in assuring that the remains of kin are treated respectfully" (1988, 6).

In our view, obtaining consent to donate fetal tissue is an ethical prerequisite for using such material to derive EG cells, even though the woman or couple are not research subjects per se, and even though the cadaveric fetus is not a human subject. This view is consistent with the conclusion of the Human Fetal Tissue Transplantation Research Panel, which held that "[e]xpress donation by the pregnant woman after the abortion decision is the most appropriate mode of transfer of fetal tissues because it is the most congruent with our society's traditions, laws, policies, and practices, including the Uniform Anatomical Gift Act and current Federal research regulations" (1988, 6). According to this panel, a woman's choice of a legal abortion does not disqualify her legally and should not disqualify her morally from serving "as the primary decisionmaker about the disposition of fetal remains, including the donation of fetal tissue for research." She "has a special connection with the fetus and she has a legitimate interest in its disposition and use." In addition, her decision to donate fetal tissue would not violate the dead fetus's interests. The panel concluded that "in the final analysis, any mode of transfer other than maternal donation appears to raise more serious ethical problems" (6). Fetal tissue should not be used without the woman's consent. Not only should her consent be necessary, it should also be sufficient to donate the tissue, except where the father's objection is known.

We concur with the Human Fetal Tissue Transplantation Research Panel that a woman undergoing an elective abortion should be authorized to donate fetal tissue, unless the father is known to object. We further agree with the panel and with subsequent federal legislation that it is important to establish safeguards to separate the pregnant woman's decision to abort from the decision to donate cadaveric fetal tissue. The guidelines already in place for fetal tissue transplantation research generally are appropriate and appear to be sufficient if they also apply to research involving human EG cells.

As already noted, some opponents of elective abortion can support fetal tissue research as long as there are safeguards to avoid direct causal responsibility and to reduce the likelihood of indirect causal responsibility. Many who view elective abortion as morally problematic, even if not always morally unjustified, also may endorse

these safeguards as a way to avoid certain forms of association with morally problematic actions and at the same time as a way to prevent the exploitation and coercion of pregnant women. Even those who do not find elective abortions morally problematic may accept these safeguards in order to protect pregnant women from exploitation and coercion as well as to sustain social practices that reflect important social and cultural values and to respect the moral concerns of opponents of elective abortion. We believe, therefore, that there can be wide agreement on appropriate safeguards for the process of donating cadaveric fetal tissue.

At a minimum, these safeguards should separate the decision to have an abortion from the decision to donate by ensuring, as much as possible, that the former occurs before the latter by not providing before the abortion decision is made information about the possibility of using fetal materials in research and by prohibiting the provision of financial compensation for the fetal tissue to the woman (or to the couple) having the abortion. If these and other requirements that already have been adopted in regulations governing federally funded human fetal tissue transplantation research do not clearly extend to research to generate EG cells from cadaveric fetal tissue, the regulations should be modified to do so.

Research with ES Cells Derived from Embryos Remaining After Infertility Treatments

Ethical issues arising from research involving the use of human embryos have generated a sustained public policy discussion and a valuable body of literature that spans at least 20 years. Some of these issues were considered in depth by the Department of Health, Education and Welfare (DHEW) Ethics Advisory Board (EAB) in 1978 and in 1979 (DHEW Ethics Advisory Board 1979). The ethical debate was continued here and abroad by other national advisory bodies, including the British Warnock Committee (Committee of Inquiry 1984) and the Canadian Royal Commission on New Reproductive Technologies (1993). In 1994, the NIH Human Embryo Research Panel considered multiple types of present and future human embryo research and discussed both ethical and public policy issues (NIH 1994). In contrast, for example, SCNT has been seriously debated in the United States and elsewhere only for about two years, and the research use of SCNT has been debated for an even shorter period.

One source of embryos for ES cells is those remaining after infertility treatments. Couples who provide such embryos have decided that they no longer need them to achieve their reproductive goals. If the couple prefers to discontinue storing the remaining embryos and does not wish to donate them to other couples, the only alternatives are to direct that the embryos be discarded (that is, to destroy them through the thawing process) or to donate them for research. When only these latter two alternatives remain, the situation is somewhat similar to that in which a woman is deciding whether to donate fetal tissue for research following elective abortion and the situation in which families are deciding whether to donate the organs or tissues of a loved one who has recently died. However, whether this similarity is decisive depends upon one's perception of the moral status of embryos. Derivation of ES cells involves destroying the embryos, whereas abortion precedes the donation of the fetal tissue and death precedes the donation of whole organs for transplantation.

The Moral Status of Embryos

To say that an entity has "moral status" is to say something both about how one should act towards that thing or person and about whether that thing or person can expect certain treatment from others. The debate about the moral status of embryos traditionally has revolved around the question of whether the embryo has the same moral status as children and adult humans do—with a right to life that may not be sacrificed by others for the benefit of society. At one end of the spectrum of attitudes is the view that the embryo is a mere cluster of cells that has no more moral status than any other collection of human cells. From this perspective, one might conclude that there are few, if any, ethical limitations on the research uses of embryos.

At the other end of the spectrum is the view that embryos should be considered in the same moral category as children or adults. According to this view, research involving the destruction of embryos is absolutely prohibited. Edmund D. Pellegrino, a professor of bioethics at Georgetown University, described this perspective in testimony given before the Commission:

> The Roman Catholic perspective...rejects the idea that full moral status is conferred by degrees or at some arbitrary point in development. Such arbitrariness is liable to definition more in accord with experimental need than ontological or biological reality.[4]

In contrast, scholars representing other religious traditions testified that moral status varies according to the stage of development.[5] For example, Margaret Farley, a professor of Christian ethics at Yale University, pointed out that

> There are clear disagreements among Catholics—whether moral theologians, church leaders, ordinary members of the Catholic community—on particular issues of fetal and embryo research....A growing number of Catholic moral theologians, for example, do not consider the human embryo in its earliest stages...to constitute an individualized human entity.[6]

Other scholars from Protestant, Jewish, and Islamic traditions noted that major strands of those traditions support a view of fetal development that does not assign full moral status to the early embryo.[7] For example, Jewish scholars testified that the issue of the moral status of extra-corporeal embryos is not central to an assessment of the ethical acceptability of research involving ES cells. Rabbi Elliot Dorff noted that

> Genetic materials outside the uterus have no legal status in Jewish law, for they are not even a part of a human being until implanted in a woman's womb and even then, during the first 40 days of gestation, their status is 'as if they were water.' As a result, frozen embryos may be discarded or used for reasonable purposes, and so may stem cells be procured from them.[8]

As a result, for some Jewish thinkers, the derivation and use of ES cells from embryos remaining after infertility treatments may be less problematic than the use of aborted fetal tissue, at least following morally unjustified abortions.

On this issue, the Commission adopted what some have described as an intermediate position, one with which many likely would agree: that the embryo merits respect as a form of human life, but not the same level of respect accorded persons. We recognize that, on such a morally contested issue, there will be strong differences of opinion. Moreover, it is unlikely that, by sheer force of argument, those with particularly strong beliefs on either side will be persuaded to change their opinions (Murray 1996). However, there is, in our judgment, considerable value in describing some of these positions, not only to reveal some of the difficulties of resolving the issue, but to seek an appropriate set of recommendations that can reflect the many values we share as well as the moral views of those with diverse ethical commitments.

A standard approach taken by those who deny that embryos are persons with the same moral status as children and adults is to identify one or more psychological or cognitive capacities that are considered essential to personhood (and a concomitant right to life) but that embryos lack. Most commonly cited are consciousness, self-consciousness, and the ability to reason (Feinberg 1986; Tooley 1983; Warren 1973). The problem with such accounts is that they appear to be either under- or over-inclusive, depending on which capacities are invoked. For example, if one requires self-consciousness or the ability to reason as an essential condition for personhood, most very young infants will not be able to satisfy this condition. On the other hand, if sentience is regarded as the touchstone of the right to life, then nonhuman animals also possess this right.

Those who deny that embryos have the same moral status as persons might maintain that the embryo is simply too nascent a form of human life to merit the kind of respect accorded more developed humans. However, some would argue that, in the absence of an event that decisively (i.e., to everyone's satisfaction) identifies the first stage of human development—a stage at which destroying human life is morally wrong—it is not permissible to destroy embryos.

The fundamental argument of those who oppose the destruction of human embryos is that these embryos are human beings and, as such, have a right to life. The very humanness of the embryo is thus thought to confer the moral status of a person. The problem is that, for some, the premise that all human lives at any stage of their development are persons in the moral sense is not self-evident. Indeed, some believe that the premise conflates two categories of human beings: namely, beings that belong to the species *homo sapiens*, and beings that

belong to a particular moral community (Warren 1973). According to this view, the fact that an individual is a member of the species *homo sapiens* is not sufficient to confer upon it membership in the moral community of persons. Although it is not clear that those who advance this view are able to establish the point at which, if ever, embryos first acquire the moral status of persons, those who oppose the destruction of embryos likewise fail to establish, in a convincing manner, why society should ascribe the status of persons to human embryos.

It is not surprising that these different views on the moral status of the embryo appear difficult to resolve, given their relationship to the issues surrounding the abortion debate, a debate the philosopher Alastair MacIntyre describes as interminable: "I do not mean by this just that such debates go on and on and on—although they do—but also that they can apparently find no terminus. There seems to be no rational way of securing moral agreement in our culture" (1984, 6). This difficulty has led most concerned observers to search for a position that respects the moral integrity of different perspectives, but to the extent possible, focuses public policy on ethical values that may be broadly shared.

The Importance of Shared Views

Once again, we are aware that the issue of the moral status of the embryo has occupied the thoughtful attention of previous bodies deliberating about fetal tissue and embryo research.[9] Further, as already noted, we do not presume to be in a position to settle this debate, but instead have aimed to develop public policy recommendations regarding research involving the derivation and use of ES cells that are formulated in terms that people who hold differing views on the status of the embryo can accept. As Thomas Nagel argues, "In a democracy, the aim of procedures of decision should be to secure results that can be acknowledged as legitimate by as wide a portion of the citizenry as possible" (1995, 212). In this vein, Amy Gutmann and Dennis Thompson argue that the construction of public policy on morally controversial matters should involve a "search for significant points of convergence between one's own understandings and those of citizens whose positions, taken in their more comprehensive forms, one must reject" (1996, 85).

R. Alta Charo suggests an approach for informing policy in this area that seeks to accommodate the interests of individuals who hold conflicting views on the status of the embryo. Charo argues that the issue of moral status can be avoided altogether by addressing the proper limits of embryo research in terms of political philosophy rather than moral philosophy:

> The political analysis entails a change in focus, away from the embryo and the research and toward an ethical balance between the interests of those who oppose destroying embryos in research and those who stand to benefit from the research findings. Thus, the deeper the degree of offense to opponents and the weaker the opportunity for resorting to the political system to impose their vision, the more compelling the benefits must be to justify the funding (1995, 20).

In Charo's view, once one recognizes that the substantive conflict among fundamental values surrounding embryo research cannot be resolved in a manner that will satisfy all sides, the most promising approach is to seek to balance all the relevant considerations in determining whether to proceed with the research. Thus, although it is clear that embryo research would offend some people deeply, she would argue that the potential health benefits for this and future generations outweigh the pain experienced by opponents of the research.

It is, however, questionable whether Charo's analysis successfully avoids the issue of moral status. It might be argued, for example, that placing the lives of embryos in this kind of utilitarian calculus will seem appropriate only to those who presuppose that embryos do not have the status of persons. Those who believe—or who genuinely allow for the possibility—that embryos have the status of persons will regard such consequentialist grounds for destroying embryos as extremely problematic.

In our view, an appropriate approach to public policy in this arena is to develop policies that demonstrate respect for all reasonable alternative points of view and that focus, when possible, on the shared fundamental values that these divergent opinions, in their own ways, seek to affirm. This particular perspective was recommended by Patricia King in her testimony before the Commission and elsewhere (1997).[10] As long as the

disagreement is cast strictly as one between those who think the embryo is a person with a right to life and those who think it has little or no moral status, the quest for convergence will be an elusive one. But there are grounds for supposing that this may be a misleading depiction of the conflict. Indeed, there may be a sufficiently broad consensus regarding the respect to be accorded to embryos to justify, under certain conditions, not only the research use of stem cells but also the use of embryos remaining after infertility treatments to generate ES cells.

The abortion debate offers an illustration of the complex middle ground that might be found in ethically and politically contentious areas of public policy. Philosopher Ronald Dworkin maintains that, despite their rhetoric, many who oppose abortion do not actually believe that the fetus is a person with a right to life. This is revealed, he claims, through a consideration of the exceptions that they often permit to their proposed prohibitions on abortion.

For example, some hold that abortion is morally permissible when a pregnancy is the result of rape or incest. Yet, as Dworkin comments, "[i]t would be contradictory to insist that a fetus has a right to live that is strong enough to justify prohibiting abortion even when childbirth would ruin a mother's or a family's life, but that ceases to exist when the pregnancy is the result of a sexual crime of which the fetus is, of course, wholly innocent" (1994, 32).

The importance of reflecting on the meaning of such exceptions in the context of the research uses of embryos is that they suggest that even in an area of great moral controversy it may be possible to identify some common ground. If it is possible to find common ground in the case of elective abortions, we might be able to identify when it would be permissible in the case of destroying embryos. For example, conservatives allow such exceptions implicitly hold with liberals that very early forms of human life may sometimes be sacrificed to promote the interests of other humans.[11] Although liberals and conservatives disagree about the range of ends for which embryonic or fetal life may ethically be sacrificed, they may be able to reach some consensus. Conservatives who accept that destroying a fetus is permissible when necessary to save a pregnant woman or spare a rape victim additional trauma might agree with liberals that it also is permissible to destroy embryos when it is necessary to save lives or prevent extreme suffering. We recognize, of course, that these cases are different, as the existence of the fetus may directly conflict with the pregnant woman's interests, while a particular *ex utero* embryo does not threaten anyone's interests. But this distinction obscures the fact that these two cases share an implicit attribution of greater value to the interests of children and adults.

We believe that the following would seem to be a reasonable statement of the kind of agreement that could be possible on this issue:

> Research that involves the destruction of embryos remaining after infertility treatments is permissible when there is good reason to believe that this destruction is necessary to develop cures for life-threatening or severely debilitating diseases and when appropriate protections and oversight are in place in order to prevent abuse.

Given the great promise of ES cell research for saving lives and alleviating suffering, such a statement would appear to be sufficient to permit, at least in certain cases, not only the use of ES cells in research, but also the use of certain embryos to generate ES cells. Some might object, however, that the benefits of the research are too uncertain to justify a comparison with the conditions under which one might make an exception to permit abortion. But the lower probability of benefits from research uses of embryos is balanced by a much higher ratio of potential lives saved relative to embryonic lives lost and by two other characteristics of the embryos used to derive ES cells: first, that they are at a much earlier stage of development than is usually true of aborted fetuses, and second, that they are about to be discarded after infertility treatment and thus have no prospect for survival even if they are not used in deriving ES cells. In our view, the potential benefits of the research outweigh the harms to embryos that are destroyed in the research process.

Another objection is that the availability of alternative means of obtaining (and sources of) stem cells makes it unnecessary to use embryos to obtain ES cells for research. Richard Doerflinger of the National Conference

of Catholic Bishops testified before the Commission that "it is now clearer than ever that new research involving adult stem cells...offers the promise that embryonic stem cells may simply be irrelevant to future medical progress."[12] In our judgment, the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research. But as we have noted, ES cells from embryos appear to be different in scientifically important ways from AS cells and also appear to offer greater promise of therapeutic breakthroughs. The claim that there are alternatives to using stem cells derived from embryos is not, at the present time, supported scientifically. We recognize, however, that this is a matter that must be revisited continually as science advances.

Nevertheless, if research is to proceed with the derivation and use of ES cells from embryos that remain following infertility treatments, we must consider what kinds of conditions and constraints should apply to this work. Many of these conditions, discussed below, also are reflected in our recommendations that are provided in the next chapter.

First, ideally, those who have the authority to decide about the disposition of the remaining embryos should make the decision about whether to donate them to another couple, to continue to store them, or to destroy them before they are asked about donating them for research. This will reduce the likelihood that a desire to benefit research will lead to a choice to destroy the embryos. If the decision to destroy the embryos precedes the decision to donate them for research purposes, then the research use of such embryos affects only how, not whether, the destruction occurs. Obviously, this separation may not be possible, particularly because the couple may be given several options simultaneously, either at the outset of treatment for infertility or after its completion. Indeed, some infertility programs provide patients with multiple consent forms at the outset of treatment, forms that include options to donate to research, discard, or transfer any embryos that remain. But even then, it may be appropriate to view the options as consisting of donation of the embryos to another couple, their continued storage, or their destruction, with destruction of the embryos taking one of two forms—discarding them through thawing or through the process of research. If embryo destruction is permissible, then it certainly should be permissible to destroy them in a way that would generate stem cells for bona fide research.

Second, the couple's or the individual's decision to donate any remaining embryos for research should be a voluntary one, free from coercion and undue pressure. Third, donors of embryos for research should not be allowed to designate or restrict the recipients of derivative tissues or cell lines for research or therapy. Fourth, even though it is legal to sell sperm and ova, it should remain illegal to sell embryos; the demonstration of respect for embryos requires this prohibition. Fifth, only the minimum number of embryos that are needed to derive sufficient stem cells for important research should be used in this way.

Sixth, it is important to develop and widely disseminate additional professional standards of practice in reproductive medicine that will reduce the likelihood that infertility clinics will increase the numbers of embryos remaining after infertility treatments in order to increase the supply for possible research purposes. These standards could address issues such as the production of embryos, the number of embryos implanted and allowed to develop to term, and the care and handling of gametes and embryos.

Seventh, any research use of embryos or embryonic cell lines imported from outside of the country must satisfy all the regulations for the use of such materials when they are produced in the United States. Eighth, if possible, institutions, researchers, and potential recipients of therapies should be informed in some way about the source of the stem cells—perhaps by tagging the cells—so that all concerned can avoid using any cells that are believed to have been derived unethically. This last condition is intended to enable institutions, researchers, and patients to make their own conscientious choices about the acceptability of using stem cells that have been derived from ethically controversial sources.

Ethical Distinctions and Relationships Between the Derivation and Use of ES Cells Derived from Embryos Remaining After Infertility Treatments

There is significant debate regarding whether the *use* of cultures of ES cells should be regarded or treated differently from the *derivation* of such cells, given that the derivation arises from the destruction of an intact embryo. For purposes of this report, three questions will help frame this issue: First, are derivation and use ethically distinct? Second, is the use of ES cells, their derivation, or both ethically justifiable? Third, should use, derivation, or both be eligible for public funding? Here we discuss our views on the first two questions. Later in this chapter, we discuss the third question in more detail.

Even though many individuals would want to avoid the use of ES cells because of their source, the processes of derivation and use are sufficiently different to warrant being regarded as morally distinct from one another. The NIH Human Embryo Research Panel reached this conclusion as well (1994). Moreover, we heard testimony that would support this distinction.[13] However, there is vigorous debate regarding whether this distinction, even if morally relevant, is morally decisive or determinative for judgments about particular actions and public policies.

As previously discussed, most moral concerns about the derivation of ES cells from embryos that remain after infertility treatments focus on the fact that derivation involves destruction. If embryos could be destroyed by allowing them to thaw—the standard approach to discarding them—and researchers could then derive ES cells, the moral issues would be parallel to those that arise in the derivation of germ cells from aborted fetuses. Destruction and derivation could be separated in principle as well as through various practical measures. However, in practice, destruction and derivation cannot be separated; therefore, this option is not available. The question, then, is whether the use of ES cells derived in a process that destroys the embryos can be morally separated from that of derivation.

There are several possible responses. One position holds that such use is morally unacceptable because it necessarily involves association with the wrongful act of embryo destruction. Another position is that the problem of associating the use of the cells and the destruction of the embryo disappears if the destruction of the embryo is not viewed as problematic, as some traditions hold. There is no association with wrongdoing if the initial act is not on balance wrong. A third position holds that even if embryo destruction is viewed as morally wrong, there still may be ways to separate at least some uses from derivation. John Robertson suggests that there may be some circumstances in which researchers using ES cells would not be considered complicit with the destruction of embryos. He indicates, for example, that there would be no meaningful association where an investigator's "research plans or actions had no effect on whether the original immoral derivation occurred" (1999, 113).

Some commentators hold that it would be ethically justifiable, though regrettable, to use existing cell lines that were derived through unethical embryo destruction. A version of this position was suggested by Father Demetrios Demopulos, who explained his views from the perspective of Eastern Orthodoxy in testimony before the Commission:

> ...I cannot condone any procedure that threatens viability, dignity, and sanctity of that life. In my view the establishment of embryonic stem cell lines...was done at the cost of human lives. Even though not yet a human person, an embryo should not be used for or sacrificed in experimentation, no matter how noble the goal may seem.[14]

Yet, in response to a Commissioner's inquiry about whether it might still be permissible to use existing ES cell lines, Demopulos stated:

> In my opinion, yes, since the lines exist and they have some benefit. I wish they had not been derived in the way that they were but since they are there....I do not think it would be a good thing to not take advantage of [their availability].[15]

In our reflections on both the distinction and relationship between derivation and use, especially for purposes of determining ethically acceptable public policy, we were influenced by testimony that stressed how important it is for public policy to be clear and to be justified in terms that are widely understood. Individuals representing widely differing views about the moral

status of the embryo and the moral justifiability of embryo destruction offered similar testimony. For example, Gilbert Meilaender called for the Commission to avoid misleading and even deceptive language in its statement and justification of public policies, whatever those policies turned out to be, on the grounds that misleading language would be a disservice to public discourse.[16] While affirming a different view regarding the moral status of embryos and embryo destruction, Dena Davis made a similar point by stressing that public policy and its rationale should pass the "straight-face test," a test failed, in her judgment, by an interpretation of federal law that permits federal funding of research using stem cells while denying federal funding of research that involves deriving the cells themselves. According to Davis, "it is disrespectful to suggest that those who believe that human embryos are persons look the other way when embryos are destroyed to obtain stem cells as long as public funding only kicks in once the stem cells are derived." Moreover, she argued that it is "more respectful, both of individuals opposed to the research and the public discourse generally, to be explicit about what is going on here and to acknowledge the ethical if not legal linkage between embryo destruction and the deriving of stem cells."[17]

The legal opinion rendered by the Department of Health and Human Services distinguishes the current legality of providing federal funds for the downstream use of ES cells from the legality of providing funds for the derivation of these cells. Indeed, as noted in Chapter 3, our own independent legal analysis reached a similar conclusion.[18] However, because our report focuses on the ethical issues involved in human ES and EG cell research, we find that there is no inconsistency between accepting this legal analysis and, at the same time, concluding that research involving both the derivation and use of these cells can under certain circumstances be justified ethically and that federal funds should be provided for both. We examine the ethical arguments for and against funding both derivation and use after we consider another possible source of stem cells–embryos that are created solely for research.

Research with ES Cells Derived from Embryos Created Solely for Research

Ever since the NIH Human Embryo Research Panel recommended that under certain conditions embryos could be created solely for research purposes (1994), there has been an ongoing discussion about the ethical and scientific merit of such a practice. Following is a discussion of this issue as it relates to two sources of ES cells derived from embryos that are created solely for research purposes.

Embryos Created Using IVF Procedures

There are two significant arguments in favor of creating human embryos using IVF technologies solely for stem cell research: The first is that there may be an inadequate supply of embryos remaining after infertility treatments. The second is that important research that could be of great medical benefit cannot be undertaken except with well-defined embryos that are created specifically for research and/or medical purposes. However, recommending federal funding for research using or deriving ES cells from embryos expressly created for research purposes presents two ethical problems. First, unlike in the case of embryos that remain following infertility treatments, there does not appear to be sufficient societal agreement on the moral acceptability of this practice at this time. Second, it is unclear whether an adequate supply of ES cells from embryos is available to meet scientific need or whether specialized cells are needed. We do not, at this time, support the federal sponsorship of research involving the creation of embryos solely for research purposes. However, we recognize that, in the future, scientific evidence and public support for this type of stem cell research may be sufficient in order to proceed. Therefore, to promote ongoing dialogue on this topic, we offer the following discussion.[19]

The "Discarded-Created" Distinction: On the Importance of Intentions

Various parties have discussed whether there is a moral difference between conducting research on embryos created with the intention of using them for reproduction and conducting research on embryos created with the intention of using them for research (Annas,

Caplan, and Elias 1996; Capron 1999; Davis 1995; Edwards 1990). Embryos created with the intention of using them for reproduction become available for research only when it is known that they are no longer intended to be used for infertility treatments; only then are they considered discarded, and only then do they become potentially available for research. The second group of embryos—research embryos—are those that are created without the intention that they will be used for procreative purposes. Rather, they are developed solely for research purposes or to generate research and medical materials such as stem cells or other cell lines, clones, DNA sequences, or proteins.

For some observers, it is difficult to defend an ethical distinction between what one can do with an embryo that has been created solely for research purposes and what one can do with an embryo remaining from infertility treatments (Davis 1995). For others, conducting research on embryos that were originally created for reproduction but which were then discarded is far easier to justify than is research conducted on embryos that were originally created for research (Harris 1998).

An ethical intuition that seems to motivate the "discarded-created" distinction is that the act of creating an embryo for reproduction is respectful in a way that is commensurate with the moral status of embryos, while the act of creating an embryo for research is not. Embryos that are discarded following the completion of IVF treatments were presumably created by individuals who had the primary intention of implanting them for reproductive purposes. These individuals did not consider the destruction of these embryos until it was determined that they were no longer needed. By contrast, research embryos are created for use in research and, in the case of stem cell research, their destruction in the process of research. Hence, one motivation that encourages serious consideration of the "discarded-created" distinction is a concern about instrumentalization—treating the embryo as a mere object—a practice that may increasingly lead us to think of embryos generally as means to our ends rather than as ends in themselves.

The Use of SCNT to Produce ES Cells

Somatic cell nuclear transfer of a diploid nucleus into an oocyte also has been suggested as a method to generate embryos from which ES cells could be derived. If successful, tissues derived from such cells could be useful in avoiding graft rejection if the donor nucleus were taken from the eventual transplant recipient. Although fertilization of an egg with sperm *in vitro* clearly results in a human zygote that will divide to become an embryo and has the potential to develop into a human if implanted, it is less clear whether the embryo created through SCNT has that potential. Nevertheless, the fact that this technique can produce living animals such as sheep and cows strongly suggests that it is likely that the cell that results from insertion of an adult nucleus into an oocyte is a zygote and can become an embryo.

Some have argued, however, that it is not clear that a zygote produced in this manner is similar to an embryo created by fertilization, because there are significant differences in the ability to generate different animals using these techniques, and we do not understand the potential of the human cell in this context. Because it is unclear whether SCNT works equally well in all species, we do not yet know whether this technique works in humans. Currently, therefore, we are uncertain whether cells created using SCNT have the full potential to become human. Because of previous work showing the potential of SCNT to create an animal in some situations, many would argue that similar concerns about the creation of embryos for research purposes apply to embryos created by SCNT. Thus, because of moral concerns outlined above regarding the creation of life only for research purposes, this category of research is disturbing to some. In the future, however, research may define conditions under which SCNT can be carried out while culturing the cells in such a manner that the resulting cell is directed to immediately differentiate into a specific tissue, precluding further development into an embryo. Perhaps in the future, then, it will be possible to use SCNT without the creation of an embryo.

One major distinction between IVF and SCNT embryos is that while creation of embryos by IVF would only generate more embryos, generation of embryos by SCNT would generate a specific kind of cell that might be useful in treating disease by allowing autologous transplant of a specific tissue type. Thus, in balancing the moral concern over the creation of an embryo and the value to society of the SCNT embryo, the potential therapeutic uses of the resulting ES cells from SCNT embryos must be evaluated carefully. At the present time, insufficient scientific evidence exists to evaluate this potential; however, within the next several years, such information should become more abundant. We recognize that if our

recommendations are accepted, the most likely way that this information will accumulate is through research carried out in the private sector.

We are aware, however, that if the use of SCNT to create embryos for research purposes were deemed to be both scientifically and medically necessary, other ethical issues still would need to be addressed. For example, we would need to revisit the current prohibition on designating a recipient of fetal or embryonic tissue, in light of the likelihood that this would be an important motivator for producing such embryos.

The Arguments Relating to Federal Funding of Research Involving the Derivation and/or Use of ES and EG Cells

This chapter has described several issues that arise when considering the ethical acceptability of stem cell research, depending on the source of the ES or EG cells. These issues are not unique to the source of funding, however, as they could apply equally to stem cell research conducted in either the private or public sector. Because our main interest is in providing advice and guidance regarding the federal government's role in funding research that involves the derivation and/or use of ES and EG cells, we now turn to an examination of arguments both for and against such funding.

Arguments Against Federal Funding of Certain Types of Human Stem Cell Research

In our deliberations, we considered three major arguments against federal funding of certain types of stem cell research: its association with abortion and embryo destruction, objections by some citizens to having federal funds used for research they consider to be objectionable, and the possibility that federal funds could be used for research using AS cells rather than ES or EG cells. Each argument is briefly considered below.

Association with Abortion and Embryo Destruction

As discussed earlier, research in this area is controversial in part because of the belief, held by some, that there is a direct or indirect association with abortion. For those who hold this belief, federal funding of research that derives EG cells from cadaveric fetal tissue after elective abortion also would involve moral association with the act of abortion.[20] Similarly, federal funding for the use of embryos remaining after infertility treatments to obtain ES cells would involve the federal government in deliberately destroying biologically human entities.

Federal Funding for ES and/or EG Cell Research Violates the Deeply Held Moral Beliefs of Some Citizens

By funding research of this kind, opponents argue that the federal government is violating the beliefs of some citizens, including the belief that they should not be required to subsidize a practice they consider to be morally objectionable. If it is possible to achieve essentially the same legitimate public goals with a policy that does not offend some citizens' sincere moral sensibilities, it would be better to do so. Sometimes, the federal government decides not to support an activity because it would be offensive to many people and because the benefits lost from this support are minimal, either because the activity is of only marginal value or because other sponsors will ensure that a worthwhile activity receives the support it needs. Not infrequently, however, activities that produce valuable results and that are legitimate objects of government funding receive such support despite the objections raised by some taxpayers. Providing such support does not violate democratic principles or infringe on the rights of dissent of those in the minority. Of course, the existence of such strongly held dissenting views makes more necessary a careful assessment of the arguments in favor of government support of the activity.

Funding Alternative Sources of Stem Cell Research Is Morally Preferable

The Commission has considered the argument that a targeted and vigorous program that aims to develop alternative sources of human stem cells could discover ways to achieve the same therapeutic goals with the use of ethically less controversial means. As noted above and in Chapter 2, research on AS cells is still developing and should be encouraged, but on scientific grounds there is good reason to believe that ES cells will provide a more reliable source of cells that can differentiate into a variety of tissues. It also should be noted that the harvesting of AS cells is technically difficult and risky to human beings. For some types of adult cells, such as bone marrow cells,

a certain amount of pain and discomfort is involved. For other types of stem cells, such as neuronal cells from the brain, there are significant risks to the donor from the brain biopsy procedure.

Although these objections to federal funding are important, they are not decisive. Regarding the objection based on association with wrongdoing, this report joins others in supporting various safeguards in the context of abortion in order to avoid any direct causal responsibility, to reduce the likelihood of any indirect causal responsibility, and to blunt symbolic association. Our report also proposes safeguards to prevent inappropriate and unnecessary use of embryos that remain following IVF. Regarding the second objection—avoiding offense to those who are morally opposed to using embryos for this purpose—we believe that public policy should avoid such offense in cases where the costs are not great, and we propose ways in which to reduce such offense. However, in this area of moral controversy, we believe that the arguments in favor of federal funding outweigh the offense that federal funding would create for some. Finally, we agree that alternative sources of stem cells should be sought when possible and that federal funds should be allocated to finding those sources. However, at the same time, we believe that on balance the ethical and scientific arguments support pursuing important research with EG cells obtained from cadaveric fetal tissue, with ES cells from embryos remaining after infertility treatments, and with other promising alternative sources. We now turn to additional arguments that lead us to support federal funding for certain types of ES and EG cell research.

Arguments in Favor of Federal Funding for Certain Types of Stem Cell Research

One of the principal ethical justifications for public sponsorship of research with human ES and EG cells is the same as for all biomedical and behavioral research in this country: Such research has the potential to produce health benefits for individuals suffering from disease. Many of the potential benefits of research using human ES or EG cells are discussed in Chapter 2.

The appeal to the potential benefits of stem cell research provides strong moral grounds for federal support of such research, but these potential benefits are not necessarily sufficient to justify this support. The pursuit of social benefit is always subject to moral constraint. Concerns for justice and respect for the rights of individuals can trump the morally laudable pursuit of potential benefits. Such concerns also may justify additional constraints on public funding of research.

The Enhancement of Scientific Progress Through Federal Support of the Derivation of ES Cells

Although ES cell lines already exist from studies conducted in the past year, relying upon these lines or upon the few other cell lines that might be derived by private companies for basic research on human stem cells could severely limit progress in this area of science. As discussed in Chapter 2, the potential to realize the possible medical benefits of ES cells depends on additional research into the nature and properties of ES cells. There are three main scientific reasons why it is beneficial for a broader segment of the scientific community to conduct research that involves both the derivation and use of ES cells.

First, there is great scientific value in understanding the process of ES cell derivation. Basic scientists who are interested in fundamental cellular processes are likely to make important discoveries about the nature of ES cells as they derive them in the laboratory. Moreover, by funding both derivation and use, under appropriate circumstances, federally funded researchers will be able to take advantage of the knowledge that arises from a detailed understanding of the source of the materials and the methods of derivation. Experience with animal studies indicates that research that involves both the derivation and use of particular cell lines has the greatest probability of generating promising new results.

Second, the properties of ES cells differ depending upon the conditions that were used to derive them. Moreover, the conditions for derivation of human ES cells that will differentiate into all tissue types are not yet fully understood by researchers. It is clear that the conditions used for mouse ES cells do not translate directly when using cells from other mammals. There is a significant amount of basic research that needs to be done regarding the process of ES cell derivation before the benefits from cell-based therapies can be realized.

Third, ES cells in culture are not stable indefinitely. As the cells are grown in culture, irreversible changes occur in their genetic makeup. Thus, especially in the first few

years of human ES cell research, it is important to repeatedly derive ES cells to be sure that the properties of the cells that are being studied have not changed.

The Benefits of Encouraging Both Public and Private Support for ES and EG Cell Research

We anticipate that in order for stem cell research to proceed most effectively, it will require an environment in which both public and private funding will be available. Indeed, in his testimony before the Commission, David Blumenthal suggested that "since prohibition of federal funding of stem cell research will result in reliance on private companies to support almost all the investigation utilizing stem cells, the differences between industrially funded and publicly funded university investigation are pertinent to your [deliberations]."[21] Increasingly, research is being supported and conducted by industry. Support for biomedical research and development from private sector pharmaceutical and biotechnology companies now outstrips the funding from all federal sources for this research, and it is likely that the field will continue to develop even if no federal funding is forthcoming. The drug industry recently estimated that $24 billion will be spent on drug research and development in 1999, up from $2 billion in 1980 (PhRMA 1998). In light of this, some might question whether federal funding for the derivation and use of ES cells from embryos remaining from infertility treatments is necessary for future progress in this field.

We believe that a combination of federal and private sector funding is more likely to produce rapid progress in this field than would private sector funding alone. An entire cadre of researchers is likely to be drawn into this field of research through the establishment of a federal funding program. Perhaps an analogy with the field of higher education is useful. It would be possible for all college and university education in the United States to be offered solely by privately funded colleges or universities. However, the combination of publicly and privately funded schools allows the higher education system as a whole to capitalize on the unique strengths of each type of institution. Competing, yet often working together, the two types of institutions may be able to achieve levels of excellence that neither type could achieve by itself.

Synergy from a Combined Federal Effort for Research Involving Use and Derivation

Federal funding provides the opportunity for collaboration and coordination among a much larger group of researchers. Moreover, the availability of federal funding would likely increase greatly the number of scientists carrying out ES and EG cell research and thus increase the chance of important findings. Federal support for research will encourage basic research on the biology of stem cells, in addition to the product-oriented research typically supported by biotechnology firms that are focused on developing marketable products. However, in the long run, advances in the basic biology of stem cells—for example, increased understanding of the conditions and signals that lead stem cells to differentiate or of the detailed mechanisms of differentiation—are essential for therapeutic advances. Such basic research will require long-term efforts, which traditionally have been supported by NIH.*

*Commissioner Capron makes the following observations: "As described in Chapter 3 and mentioned earlier in this chapter, NIH, relying on the opinion of the General Counsel of DHHS, has concluded that the present rider to the Department's appropriation allows the funding of research using but not deriving ES cells from embryos because the latter would involve destroying embryos for research purposes. The alternative policy urged in this report would, in addition to its scientific benefits, also enable the federal government to play a stronger role in ensuring that ethically acceptable processes are used in deriving the ES cells that federally supported scientists use in their research. Specifically, adopting a limited exception to the funding ban solely to allow support of ES cell line derivation from embryos donated from fertility programs provides a stronger platform for the federal government to enforce the distinction between research using this group of embryos and that which would use embryos created solely for research purposes.

Of course, even if NIH funds only 'use' research, it could still try to require that the ES cells used not be derived from embryos created for research purposes. But its moral leverage is undermined by its own rationale: By insisting that federal funding of research using human ES cells does not implicate federal sponsors in the process by which the ES cells have been derived, it limits its ability to mandate that one process rather than another be used. Plainly, federal law could restrict federal support to activities that do not, for example, cause unlawful pollution; by extension, the limitation could extend to activities that do not purchase materials that were produced in processes that pollute. In the present case, however, the appropriations rider bans federal support for research that creates or destroys human embryos, which means that a federal agency cannot claim to be implementing federal policy were it to limit funding to research that uses only those ES cells that were derived from discarded embryos but not from embryos created for the purpose of deriving ES cells. Thus, NIH may be hard pressed to justify differentiation based on the type of embryos from which ES cells are derived, thereby losing an opportunity to oversee the derivation process directly and to enforce an important ethical distinction.

Adopting a limited exception to the embryo research ban solely for research to derive ES cells from embryos remaining from fertility programs would also avoid relying on the theoretical line between derivation and use research that underlies the NIH policy. Such a line is difficult to defend in practical terms when the question is not whether an activity is inherently licit or illicit but whether it ought to be paid for with federal research dollars. Any such line is merely theoretical because the funding provided for research using ES cells would of course flow directly to researchers deriving those cells, perhaps even in an adjacent laboratory. The only difference would be that the federal funds would not go directly as salary and laboratory expenses for the derivation process but indirectly in the form of funds to purchase the ES cells (which funds would then pay salaries, laboratory expenses, and so forth)."

Requiring That Recipients Conduct Their Research in Accordance with the Federal Regulations

As with all federally sponsored research, conditions attached to funding provide the federal government with the authority to require compliance with relevant regulations, policies, and guidelines. Among these regulations are those pertaining to human subjects research, tissue donation and transplantation, oversight, and review. In addition, federal funding agencies can stipulate that recipients of federal funding for human stem cell research must share both research results and research materials (including cell lines) with other recipients of federal funds or with all other researchers. Thus, federal funding may lead to more widespread dissemination of findings and sharing of materials, which ultimately may enhance scientific discoveries.

In contrast, many privately funded studies require that the scientists not distribute their findings until after a review by the company and that materials can be shared only after the institution receiving the materials has signed a material transfer agreement. Some of these agreements make it difficult for scientists to share or secure the reagents necessary for their research, even if they wish to do so. As the Institute of Medicine noted in its report, *Resource Sharing in Biomedical Research*, "The perception that scientific data and research materials (e.g., animals, reagents, etc.) have potential commercial value frequently causes universities to be even more reluctant than individual scientists with respect to sharing" (1996, 81).

Sustaining U.S. Leadership in Science and Technology

In supporting federal funding for certain types of stem cell research, we are not opposing research in the private sector. On the contrary, we recognize the value for the nation's investment in science and technology for research sponsored and conducted by both the public and the private sectors and the quality of private sector research. Indeed, stem cell research is receiving, and probably will continue to receive, increasing support from industry. There are, however, certain specific advantages that arise from the federal investment in science that should be acknowledged. An observation made by the Office of Technology Assessment, in its 1986 report, *Research Funding as an Investment*, is relevant in this context.

> The goal of federally funded research is not profitability, but a means of achieving social objectives, whether they are health, national security, or the enhancement of knowledge and education. The Federal research infrastructure is designed to provide a stable environment for these goals, despite a changing political environment....In addition, Federal research programs must be responsive to many more groups than industrial research efforts, and this affects the manner in which the research agenda is shaped. (1986, 61)

Federal funding is probably required in order for the United States to sustain a leadership position in this increasingly important area of research. By funding research, the federal government conveys the clear message that, under particular conditions and constraints, certain types of human stem cell research can be morally legitimate research that is worthy of public support.

Just Distribution of Potential Benefits from Stem Cell Research

Much of the testimony we heard indicated that the just distribution of the benefits of stem cell research, including both the knowledge gained and any potential therapeutic benefits, should be taken into account in any recommendation that would permit the federal government to support ES and EG cell research. For example, there was widespread agreement among the religious scholars who testified before us that in order for this research to be morally acceptable, several "background factors" must be in place, including equitable access to the benefits of the research and appropriate prioritization of this research relative to other social needs, both of which involve procedural and substantive justice. (See Appendix E.)

Issues of procedural and substantive justice are not unique to stem cell research but rather arise in various societal decisions about the use of funds for research, medical care, and other goods. Although we can note these issues here, we cannot resolve them. In addition, federal funding of stem cell research does not guarantee

that greater numbers of the American public will have access to the fruits of basic or applied research or that this will occur more quickly than it would if federal funding were not available. However, by recommending federal funding for certain types of human stem cell research, we acknowledge that there is a basis for an argument for broader access to any therapies developed from that research.

Ethical Issues in Adopting Federal Oversight and Review Policies for ES and EG Cell Research

Concerns have been expressed regarding the likelihood of accountability depending on whether ES and EG cell research is sponsored and/or conducted by the public or private sector. Arthur Caplan, a bioethicist at the University of Pennsylvania, in testimony before the Senate Subcommittee on Labor, Health and Human Services, Education and Related Agencies, said that

> ...it is better to do things in this area that are accountable and public, than it is to ask them to become private and commercial. And if we continue the policies we have, we're not going to be able to bring the nuanced supervision and oversight that this area of stem cell research requires from us....That's why we need public funding, public accountability, to make the right tradeoffs.[22]

One of the principal benefits of federal funding of biomedical and behavioral research is that it is relatively easy to put in place an effective system of public oversight and review. By oversight, we are referring to the mechanism of monitoring categories of research or other activities to determine compliance with policies, procedures, rules, guidelines, and regulations and to prevent abuses. It is a policy strategy designed to provide the appropriate checks and balances and ensure ethically acceptable research protocols. The existing federal system of oversight has its origins both in the legislative and executive branches of the federal government: Congress, through its appropriations authority, may (and often does) direct that certain research be undertaken or avoided. Seen in this way, federal oversight can provide the public with two assurances: first, that stem cell research will receive national attention and scrutiny through the appropriations process undertaken by Congress; and second, that stem cell research would be conducted in accordance with relevant federal regulations. These oversight components are necessary but not sufficient for providing the public with confidence that research, especially research involving human subjects, is being undertaken appropriately. There also are mechanisms maintained by individual agencies such as the Food and Drug Administration.

In contrast, review usually refers to the evaluation of individual research protocols involving human subjects to assess their scientific merit and ethical acceptability—the activity usually carried out by Institutional Review Boards. As noted above, however, some research involving human stem cells may not be considered research involving human subjects, as defined by the Common Rule. In our view, the considerable sensitivity and public concern regarding stem cell research merits both national and local approaches to oversight and review, the details of which are described in the following chapter. We are persuaded that federal oversight and review of some types of stem cell research is required in order to make federal funding available to support such research. The types of questions about ES and EG cell research that we consider important for such an oversight and review body to ask are enumerated in Appendix F.

Summary

We were asked by the President to thoroughly review the issues associated with stem cell research, "balancing all ethical and medical considerations." In this chapter, we have endeavored to do just that. Specifically, we recognized that there are many different views on the ethical appropriateness of this type of research and also on the appropriateness of providing federal funding for such research. We believe that the ethical arguments that support the use of federal funds for stem cell research using cadaveric fetal tissue and for both deriving and using ES cells from embryos remaining after infertility treatments have considerable merit. However, such research should be conducted only within the context of a framework of national oversight and review. At the same time, we were

not persuaded that we should recommend that federal funds be available at this time for the creation of embryos solely for research purposes. We arrived at these conclusions with full awareness of the strongly held views (from both religious and secular ethical perspectives) on all sides of the main issues regarding the morality of stem cell research.

Notes

1 The arguments presented here were helpfully informed by two papers prepared for the National Bioethics Advisory Commission (NBAC) by Fletcher, J.C., 1999, "Deliberating Incrementally on Human Pluripotential Stem Cell Research," and Siegel, A.W., 1999, "Locating Convergence: Ethics, Public Policy and Human Stem Cell Research." Both of these papers are available in Volume II of this report.

2 Eiseman, E., 1999, "Quick Response: Use of Human Fetal Tissue in Federally Funded Research." This paper was prepared for NBAC and is available in Volume II of this report.

3 Several terms have been used to refer to inappropriate connections between one agent's actions and another agent's wrongdoing. We have mainly used the term *association*, but other terms include *cooperation, collaboration,* and *complicity*. See, for example, Childress (1990). For a discussion of cooperation and complicity with evil in Roman Catholic moral theology, see Maguire (1986).

4 Pellegrino, E.D., Testimony before NBAC. May 7, 1999. Washington, DC. Meeting transcript, 10.

5 For a summary of these positions, see Appendix E.

6 Farley, M., Testimony before NBAC. May 7, 1999. Washington, DC. Meeting transcript, 18.

7 Dorff, E., M. Tendler, L. Zoloth, A. Sachedina. Testimony before NBAC. May 7, 1999. Washington, DC.

8 Dorff, E., Testimony before NBAC. May 7, 1999. Washington, DC. Meeting transcript, 48.

9 For a discussion of these issues see the paper prepared for NBAC by Knowles, L.P., 1999, "International Perspectives on Human Embryo and Fetal Tissue Research," available in Volume II of this report.

10 King, P.A., Testimony before NBAC. January 19, 1999. Washington, DC.

11 The terms *liberal* and *conservative* used here are used in the context intended by Dworkin (1994), *Life's Dominion*.

12 Doerflinger, R., Written testimony before NBAC. April 16, 1999. Charlottesville, VA. Meeting transcript, 1.

13 Pellegrino, E.D., Testimony before NBAC. May 7, 1999. Washington, DC.

14 Demopulos, D., Testimony before NBAC. May 7, 1999. Washington, DC. Meeting transcript, 89.

15 Ibid.

16 Meilaender, G., Testimony before NBAC. May 7, 1999, Washington, DC.

17 Davis, D., Testimony before NBAC. May 7, 1999. Washington, DC. Meeting transcript, 164.

18 This opinion was provided by Flannery, E., 1999, in "Analysis of Federal Laws Pertaining to Funding of Human Pluripotent Stem Cell Research," available in Volume II of this report.

19 For a discussion of these issues see the paper prepared for NBAC by Parens, E., 1999, "What Has the President Asked of NBAC? On the Ethics and Politics of Embryonic Stem Cell Research," available in Volume II of this report.

20 It is important to note, however, that the abortion exceptions, which serve as the basis for the type of shared views identified above, are exceptions to the law banning federal funding for abortions (Title V, Labor, HHS, and Education Appropriations, 112 Stat. 3681-385, Sec. 509 (a) (1)&(2)). Thus, federal funding for research use of cadaveric fetal tissue, within appropriate limits, might be viewed as consistent with current federal funding practices in the abortion context.

21 Blumenthal, D., Written testimony before NBAC. February 2, 1999. Princeton, NJ. Meeting transcript, 1.

22 Caplan, A.L., Testimony before the Senate Appropriations Subcommittee on Labor, Health, and Human Services, Education and Related Agencies. December 2, 1998.

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Chapter Five

Conclusions and Recommendations

Introduction

In November 1998, President Clinton charged the National Bioethics Advisory Commission with the task of conducting a thorough review of the issues associated with human stem cell research, balancing all ethical and medical considerations. The President's request was made in response to three separate reports that brought to the fore the exciting scientific and clinical prospects of stem cell research while also raising a series of ethical controversies regarding federal sponsorship of scientific inquiry in this area. Such research raises ethical issues because it involves the derivation of human *embryonic germ (EG) cells* from aborted fetuses or the derivation of human *embryonic stem (ES) cells* from early stage embryos remaining after infertility treatments. A number of these important ethical concerns previously have been identified in public debate, both here and abroad. The Commission reviewed these concerns in light of both the medical and scientific promise in this significant new field and the existing statutes and regulations that affect research in this area. Our task, however, was neither to engage in moral analysis for its own sake nor to address all the regulatory issues that might be raised, but rather to offer advice on how the balance of ethical, scientific, and medical considerations should shape policies on the use of federal funds to support research that involves deriving or using human ES or EG cells.

Scientific and Medical Considerations

The stem cell is a unique and essential cell type found in animals. Many kinds of stem cells are found in the human body, with some more differentiated, or committed, to a particular function than others. In other words, when stem cells divide, some of the progeny mature into cells of a specific type (heart, muscle, blood, or brain cells), while others remain stem cells, ready to repair some of the everyday wear and tear undergone by our bodies. These stem cells are capable of continually reproducing themselves and serve to renew tissue throughout an individual's life. For example, they continually regenerate the lining of the gut, revitalize skin, and produce a whole range of blood cells. Although the term *stem cell* commonly is used to refer to those cells within the adult organism that renew tissue (e.g., hematopoietic stem cells, a type of cell found in the blood), the most fundamental and extraordinary of the stem cells are found in the early stage embryo. These ES cells, unlike the more differentiated adult stem (AS) cells or other cell types, retain the special ability to develop into nearly any cell type. EG cells, which originate from the primordial reproductive cells of the developing fetus, have properties similar to ES cells.

It is the potentially unique versatility of the ES and EG cells derived, respectively, from the early stage embryo and cadaveric fetal tissue that presents such unusual scientific and therapeutic promise. Indeed, scientists have long recognized the possibility of using such cells to generate more specialized cells or tissue, which could allow the newly generated cells to be used to treat injuries or diseases such as Alzheimer's disease, Parkinson's disease, heart disease, and kidney failure. In addition, scientists regard these cells as important—perhaps essential—in understanding the earliest stages of human development and in developing life-saving drugs and cell-replacement therapies to treat disorders caused by early cell death or

impairment. At the same time, the techniques for deriving these cells have not been fully developed as standardized and readily available research tools, and the development of any therapeutic application remains some years away.

Research also is under way to determine whether human stem cells could be obtained from the differentiated stem cells of fully developed organisms. Thus far, however, studies in animals indicate that this approach faces substantial scientific and technical limitations; indeed, the anatomic source of certain cells might preclude easy or safe access in human beings. In addition, important biological differences apparently exist between ES cells, EG cells, and AS cells. Furthermore, differences among species mean that for full scientific and clinical benefits to be realized, some research will need to be conducted with human ES and EG cells, even as the emphasis remains on laboratory and animal research. In summary, research using stem cells from animals or from human adults is not a substitute for human ES and EG cell research, and it is toward the latter that we direct our ethical and policy analyses.

Ethical and Policy Considerations

The longstanding controversy about the ethics of research involving human embryos and cadaveric fetal material arises from fundamental and sharply differing moral views regarding elective abortion or the use of embryos for research. Indeed, an earnest national and international debate continues over the ethical, legal, and medical issues that arise in this arena. This debate represents both a challenge and an opportunity: a challenge because it concerns important and morally contested questions regarding the beginning of life, and an opportunity because it provides another occasion for serious public discussion about important ethical issues. We are hopeful that this dialogue will foster public understanding about the relationships between the opportunities that biomedical science offers to improve human welfare and the limits set by important ethical obligations.

Although we believe most would agree that human embryos deserve respect as a form of human life, disagreements arise regarding both what form such respect should take and what level of protection is required at different stages of embryonic development. Therefore, embryo research that is not therapeutic to the embryo is bound to raise serious concerns for some about how to resolve the tensions between two important ethical commitments: to cure disease and to protect human life. For those who believe that from the moment of conception the embryo has the moral status of a person, research (or any other activity) that would destroy the embryo is considered wrong and should be prohibited. For those who believe otherwise, arriving at an ethically acceptable policy in this arena involves a complex balancing of many important ethical concerns. Although many of the issues remain contested on moral grounds, they can exist within a broad area of consensus upon which public policy can, at least in part, be constructed.

For most observers, the resolution of these ethical and scientific issues depends to some degree upon the source of the stem cells. The use of cadaveric fetal tissue to derive EG cell lines—like other uses of tissues or organs from dead bodies—is generally the most acceptable of these sources, provided that the research complies with the system of public safeguards and oversight already in place for such scientific inquiry. With respect to embryos and the ES cells from which they can be derived, some draw an ethical distinction among three potential types of embryos. One is referred to as the *research embryo*, an embryo created through *in vitro* fertilization (IVF), with gametes provided solely for research purposes. Many people, including the President, have expressed the view that the federal government should not fund research that involves creating such embryos. The second type of embryo is that which was created for treatment of infertility, but is now intended to be discarded because it is unsuitable or no longer needed for such treatment. The use of these embryos raises fewer ethical questions because it does not alter their final disposition. Finally, the recent demonstration of cloning techniques (somatic cell nuclear transfer [SCNT]) in nonhuman animals suggests that the transfer of a human somatic cell nucleus into an oocyte might create an embryo that could be used as a source of ES cells. The creation of a human organism using this technique raises questions similar to those raised by the creation of research embryos through IVF, and at this time federal funds may not be used for such

research. In addition, if the enucleated oocyte that was to be combined with a human somatic cell nucleus came from a nonhuman animal, other issues would arise about the nature of the embryo produced. Thus, each source of material raises distinct ethical questions as well as scientific, medical, and legal ones.

Conscientious individuals have reached different conclusions regarding both public policy and private actions in the area of stem cell research. Their differing perspectives by their very nature cannot easily be bridged by any single public policy. But the development of such policy in a morally contested area is not a novel challenge for a pluralistic democracy such as that which exists in the United States. We are profoundly aware of the diverse and strongly held views on the subject of this report and has wrestled with the implications of these different views at each of our meetings devoted to this topic. Our aim throughout these deliberations has been to formulate a set of recommendations that fully reflects widely shared views and that, in our view, would serve the best interests of society.

Most states place no legal restrictions on any of the means of creating ES and EG cells that are described in this report. In addition, current Food and Drug Administration (FDA) regulations do not apply to this type of early stage research. (See Appendix D.) Therefore, because the public controversy surrounding such activities in the United States has revolved around whether it is appropriate for the federal government to sponsor such research, this report focuses on the question of whether the scientific merit and the substantive clinical promise of this research justify federal support, and, if so, with what restrictions and safeguards.

Views about the status of embryos and fetuses vary widely. Some believe that what matters is the potential for a new human life that arises at the moment of conception, while others identify the relevant concept as personhood, which they say begins only at some postembryonic stage. We heard from many members of the public, including those who are eager for this area of research to move forward as rapidly as possible, as well as those who oppose the research if it is built upon any activity that is connected to abortion or to the destruction of fertilized human eggs. In addition, our deliberations have been informed by testimony from scientists and physicians, lawyers and other experts in governmental regulation, philosophers, and Catholic, Protestant, Jewish, Islamic, and Eastern Orthodox theologians. As a result of these discussions, it has become clear that the question of whether federal policy should sponsor human ES or EG cell research is characterized by a tension between the desire to realize the great therapeutic benefits that may be derived from such work and the need to recognize that the materials involved must be treated with respect. We concluded that sufficient safeguards can be put in place in order to prevent abuse and to ensure that any use of embryos that remain after infertility treatments—like any use of fetal remains following elective abortion—is based upon and embodies the kind of respect for the embryos that most Americans would expect and demand of any activity that is carried out with the support of the federal government. Beyond the regulatory effects of the rules adopted to govern federal support for research in this area—with which we hope private sponsors of research involving ES and EG cells will comply voluntarily—the states also can influence research in this field through statutes and regulations on abortion, embryo research, and the donation of human body parts, embryos, and gametes.

Conclusions and Recommendations

The conclusions and recommendations presented in this chapter are grouped into several categories:

- the ethical acceptability of federal funding for research that either derives or uses ES or EG cells,
- the requirements for the donation of cadaveric fetal tissue and embryos for research,
- restrictions on the sale of these materials and designation of those who may benefit from their use,
- the need—and the means—for national oversight and institutional review,
- the need for local review of derivation protocols,
- the responsibilities of federal research agencies,
- the issues that must be considered regarding the private sector, and
- the need for ongoing review and assessment.

The Ethical Acceptability of Federal Funding of ES Cell and EG Cell Research

Despite the enormous scientific and clinical potential offered by research use of ES or EG cells derived from various sources, many find that certain sources are more ethically problematic than others. Our recommendations reflect respect for these diverse views, which varied even among the Commissioners, regarding the ethical acceptability of the derivation and use of ES and EG cells from various sources.

As described in Chapter 2, human ES and EG cells can be derived from the following sources:

- human fetal tissue following elective abortion (EG cells),
- human embryos that are created by IVF and that are no longer needed by couples being treated for infertility (ES cells),
- human embryos that are created by IVF with gametes donated for the sole purpose of providing research material (ES cells), and
- potentially, human (or hybrid) embryos generated asexually by SCNT or similar cloning techniques in which the nucleus of an adult human cell is introduced into an enucleated human or animal ovum (ES cells).

A principal ethical justification for public sponsorship of research with human ES or EG cells is that this research has the potential to produce health benefits for those who are suffering from serious and often fatal diseases. We recognize that it is possible that all the various sources of human ES or EG cells eventually could be important to research and clinical application because of, for example, their differing proliferation potential, differing availability and accessibility, and differing ability to be manipulated, as well as possibly significant differences in their cell biology.

Although each source of stem cells poses its own scientific, ethical, and legal challenges and opportunities, much of the ethical analysis leading to public policy recommendations depends upon the scientific and/or clinical necessity of using a specific source of the cells. In our judgment, the immediate scientific uses of ES or EG cells can be satisfied by the derivation and use of cell lines derived from fetal tissues (i.e., EG cells) and from embryos (i.e., ES cells) remaining after infertility treatments have ended.

The potential use of matched tissue for autologous cell-replacement therapy from ES cells may in the future require the use of cell lines developed by SCNT techniques. In addition, embryos created through IVF specifically as a source of ES cells might be essential for creating banks of multiple cell lines representing a spectrum of alleles for the major histocompatibility complex. This goal might require that ova and sperm of persons with specific genotypes be selected to make embryos from which to derive particular classes of ES cells.

Finally, although much promising research currently is being conducted with stem cells obtained from adult organisms, studies in animals suggest that this approach will be scientifically and technically limited, and, in some cases, the anatomic source of the cells might preclude easy or safe access. Important research can and should go forward in this area, although important biological differences exist between ES and AS cells, and the use of AS cells should not be considered an alternative to ES and EG cell research.

Much research into the generation of specific tissue types from stem cells can be conducted using EG cells derived from fetal material and ES cells derived from embryos remaining after infertility treatments. In the future, adequate scientific evidence and increased prospect for medical benefits may be available to generate public support for using human ES cells derived from embryos produced through IVF for research purposes or by SCNT for autologous transplant. We note, however, that a responsible federal science policy does not necessarily require public funding for access to all sources of ES or EG cells at once. **At this time, therefore, the Commission believes that federal funding for the use and derivation of ES and EG cells should be limited to two sources of such material: cadaveric fetal tissue and embryos remaining after infertility treatments.** Specific recommendations and their justifications are provided below.

Recommendation 1:

Research involving the derivation and use of human EG cells from cadaveric fetal tissue should continue to be eligible for federal funding. Relevant statutes and regulations should be amended to make clear that the ethical safeguards that exist for fetal tissue transplantation also

apply to the derivation and use of human EG cells for research purposes.

Considerable agreement exists, both in the United States and throughout the world, that the use of fetal tissue in therapy for those with serious disorders, such as Parkinson's disease, is acceptable.[1] Research that uses cadaveric tissue from aborted fetuses is analogous to the use of fetal tissue in transplantation. The rationales for conducting EG research are equally strong, and the arguments against it are not persuasive. The removal of fetal germ cells does not occasion the destruction of a live fetus, nor is fetal tissue intentionally or purposefully created for human stem cell research. Although abortion itself doubtless will remain a contentious issue in our society, the procedures that have been developed to prevent fetal tissue donation for therapeutic transplantation from influencing the abortion decision offer a model for creating such separation in research to derive human EG cells. Because the existing statutes are written in terms of tissue transplantation, which is not a current feature of EG cell research, changes are needed to make explicit that the relevant safeguards will apply to research to derive EG cells from aborted fetuses.

Due to the contentious and polarizing nature of the abortion debate in the United States, restrictions were enacted over a decade ago to block the use of federal funding of fetal tissue transplantation therapy research. Until 1993, the only permissible source of tissue for such research was tissue from spontaneously aborted fetuses or ectopic pregnancies—sources that were largely unsuitable for research. In 1993, President Clinton lifted the ban on the use of fetal tissue from elective abortions for fetal tissue transplantation research.

Previous moral opposition to fetal tissue transplant research, because of its association with abortion, helped shape a system of safeguards to prevent the encouragement of the practice. These rules require that the consent process for women making abortion decisions must precede separately from the consent process for donation of fetal tissue for transplant research. Although some disagree, sufficient consensus exists that society should respect the autonomous choices of women who have chosen to have legal abortions to donate fetal tissue for research. If women have a right to choose to have an abortion, it follows that the self-determination or autonomy expressed in that right extends to the choice to donate fetal tissue for research purposes.

Research using fetal tissue obtained after legal elective abortions will greatly benefit biomedical science and also will provide enormous therapeutic benefits to those suffering from various diseases and other conditions. In our view, there is no overriding reason for society to discourage or prohibit this research and thus forgo an important opportunity to benefit science and those who are suffering from illness and disease—especially in light of the legality of elective abortions that provide access to fetal tissue and of the risks involved in losing these valuable opportunities. Indeed, the consequences of forgoing the benefits of the use of fetal tissue may well be harmful. Moreover, if not used in research, this tissue will be discarded.

The Acceptability of Federal Support for Research Using Embryos Remaining After Infertility Treatments to Derive ES Cells

The current congressional ban on embryo research prohibits federal support of any research "in which a human embryo...[is] destroyed, discarded, or knowingly subjected to risk of injury greater than that allowed for research on fetuses *in utero*."[2] The term *human embryo* in the statute is defined as "any organism, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."

The ban, which concerns only federally sponsored research, reflects a moral stance either that embryos deserve some measure of protection from society because of their moral status as persons, or that sufficient public controversy exists such that federal funds should not be used for this type of research. However, some effects of the embryo research ban raise serious moral and public policy concerns for those who hold differing views of the ethics of embryo research. In our view, the ban conflicts with several of the ethical goals of medicine, especially healing, prevention, and research—goals that are rightly characterized by the principles of beneficence and nonmaleficence, jointly encouraging the pursuit of each social benefit and avoiding or ameliorating potential harm.

In the United States, moral disputes—especially those concerning certain practices in the area of human reproduction—are sometimes resolved by denying federal

funding for those practices (e.g., elective abortion), while not interfering with the practice in the private sector. In this case, investigative embryo research guided only by self-regulation is a widespread practice in the private sector, and the ban on embryo research has served to discourage the development of a coherent public policy, not only regarding embryo research but also regarding health research more generally. The ban also may have more profound effects on other areas of federally supported research that are dedicated to the relief of human suffering, raising concerns about the distribution and allocation of federal research resources. For example, by limiting the federal government's ability to fund promising areas of basic research, a complete ban on embryo research could prevent promising, collaborative studies in other areas, such as cancer and genetics. We recognize that many factors affect how federal research priorities are set in this country. However, in our view, the intentional withholding of federal funds for research that may lead to promising treatments may be considered unjust or unfair.

Although no consensus has been reached regarding the moral status of the embryo, there is agreement that if embryo research is permissible, some limitations and/or regulations are necessary and appropriate. Such regulation reflects an appreciation of the disparate views regarding the acceptability and unacceptability of this area of scientific investigation and serves as a way of providing accountability, allaying public anxiety, promoting beneficial research, and demonstrating respect for human embryos.

Recommendation 2:

Research involving the derivation and use of human ES cells from embryos remaining after infertility treatments should be eligible for federal funding. An exception should be made to the present statutory ban on federal funding of embryo research to permit federal agencies to fund research involving the derivation of human ES cells from this source under appropriate regulations that include public oversight and review. (See Recommendations 5 through 9.)

Based on advice from the Department of Health and Human Services (DHHS) General Counsel, the Director of the National Institutes of Health (NIH) announced in January 1999 that NIH will apply the ban only to research involving the derivation of ES cells from human embryos but not to research involving only the use of ES cells. NIH has indicated that research proposals that involve the use of ES cells will be considered for funding once NIH has established a set of special guidelines that are currently under development. The DHHS General Counsel concluded that ES cells are not, in themselves, organisms and hence cannot be embryos as defined by the statute. Thus, it could be surmised from this interpretation that the only activity that could amount to "research in which a human embryo or embryos are destroyed" would be an attempt to derive ES cells from living embryos. This, in fact, is the interpretation adopted by DHHS and NIH. More than 70 members of Congress have protested this interpretation, claiming that whatever the language of the statute, Congress clearly intended to prohibit not just research in which human embryos are destroyed but also research that depends on the prior destruction of a human embryo. Yet the plain meaning of the statutory wording differs from this interpretation, and nothing in its legislative history indicates that either proponents or opponents of the rider anticipated a situation in which research that destroyed the embryo would be conducted separately from research that used the cells derived from the embryo. Thus, in legal terms, the General Counsel's interpretation appears to be reasonable, even though it does not address any of the ethical concerns involved.

Although some may view the derivation and use of ES cells as ethically distinct activities, we believe that it is ethically acceptable for the federal government to finance research that both derives cell lines from embryos remaining after infertility treatments and that uses those cell lines. Although one might argue that some important research could proceed in the absence of federal funding for research that derives stem cells from embryos remaining after infertility treatments (i.e., federally funded scientists merely using cells derived with private funds), we believe that it is important that federal funding be made available for protocols that also derive such cells. Relying on cell lines that might be derived exclusively by a subset of privately funded researchers who are

interested in this area could severely limit scientific and clinical progress.

An ethical problem is presented in trying to separate research in which human ES cells are used from the process of deriving those cells, because doing so diminishes the scientific value of the activities receiving federal support. This division—under which neither biomedical researchers at NIH nor scientists at universities and other research institutions who rely on federal support could participate in some aspects of this research—rests on the mistaken notion that derivation and use can be neatly separated without affecting the expansion of scientific knowledge. We believe that this misrepresentation of the new field of human stem cell research has several implications.

First, researchers using human ES cell lines will derive substantial scientific benefits from a detailed understanding of the process of ES cell derivation, because the properties of ES cells and the methods for sustaining the cell lines may differ depending upon the conditions and methods used to derive them. Thus, scientists who conduct basic research and who are interested in fundamental cellular processes are likely to make elemental discoveries about the nature of ES cells as they derive them in the laboratory. Second, significant basic research must be conducted regarding the process of ES cell derivation before cell-based therapies can be fully realized, and this work must be pursued in a wide variety of settings, including those exclusively devoted to basic academic research. Third, ES cells are not indefinitely stable in culture. As these cells are grown, irreversible changes occur in their genetic makeup. Thus, especially in the first few years of human ES cell research, it is important 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.

Thus, anyone who believes that federal support of this important new field of research should maximize its scientific and clinical value within a system of appropriate ethical oversight should be dissatisfied with a position that allows federal agencies to fund research using human ES cells but not research through which the cells are derived from embryos. Instead, recognizing the close connection in practical terms between the derivation and the use of these cells, it would be preferable to enact provisions that apply to funding by all federal agencies, provisions that would carve out a narrow exception for funding of research to use or to derive human ES cells from embryos that would otherwise be discarded by infertility treatment programs.

The Ethical Acceptability of Creating Embryos Through IVF Specifically as a Source of ES Cells

ES cells can be obtained from human research embryos created from donor gametes through IVF for the sole purpose of deriving such cells for research. The primary objection to creating embryos specifically for research is that many believe that there is a morally relevant difference between producing an embryo for the sole purpose of creating a child and producing an embryo with no such goal. Those who object to creating embryos for research often appeal to arguments that speak to respecting human dignity by avoiding the instrumental use of human embryos (i.e., using embryos merely as a means to some other goal does not treat them with appropriate respect or concern as a form of human life). Currently, we believe that cadaveric fetal tissue and embryos remaining after infertility treatments provide an adequate supply of research resources for federal research projects involving human embryos. Therefore, embryos created specifically for research purposes are not needed at the current time in order to conduct important research in this area.

Recommendation 3:

Federal agencies should not fund research involving the derivation or use of human ES cells from embryos made solely for research purposes using IVF.

In 1994, the NIH Human Embryo Research Panel argued in support of federal funding of the creation of embryos for research purposes in exceptional cases, such as the need to create banks of cell lines with different genetic make-ups that encoded various transplantation antigens—the better to respond, for example, to the transplant needs of groups with different genetic profiles. Such a project would require the recruitment of embryos from genetically diverse donors.

A number of points are worth considering in determining how to deal with this issue. First, it is possible that the creation of research embryos will provide the only opportunity to conduct certain kinds of research—such as research into the process of human fertilization. Second, as IVF techniques improve, it is possible that the supply of embryos for research from this source will dwindle. Nevertheless, we have concluded that, either from a scientific or a clinical perspective, there is no compelling reason to provide federal funds for the creation of embryos for research at this time.

The Use of SCNT to Obtain ES Cells

The use of SCNT to transfer the nucleus of an adult somatic cell into an enucleated human egg likely has the potential of creating a human embryo. To date, although little is known about these embryos as potential sources of human ES cells, there is significant reason to believe that their use may have therapeutic potential. For example, the possible use of matched tissue for autologous cell-replacement therapy from ES cells may require the use of SCNT. Arguably, the use of this technique to create an embryo is different from the other cases we have considered—because of the asexual origin of the source of the ES cells—although oocyte donation is necessarily involved. We conclude that at this time, because other sources are likely to provide the cells needed for the preliminary stages of research, federal funding should not be provided to derive ES cells from SCNT. Nevertheless, the medical utility and scientific progress of this line of research should be monitored closely.

Recommendation 4:

Federal agencies should not fund research involving the derivation or use of human ES cells from embryos made using SCNT into oocytes.

Requirements for the Donation of Cadaveric Fetal Tissue and Embryos for Research

Potential donors of embryos for ES cell research must be able to make voluntary and informed choices about whether and how to dispose of their embryos. Because of concerns about coercion and exploitation of potential donors, as well as controversy regarding the moral status of embryos, it is important, whenever possible, to separate donors' decisions to dispose of their embryos from their decisions to donate them for research. Potential donors should be asked to provide embryos for research only if they have decided to have those embryos discarded instead of donating them to another couple or storing them. If the decision to discard the embryos precedes the decision to donate them for research purposes, then the research determines only how their destruction occurs, not whether it occurs.

Recommendation 5:

Prospective donors of embryos remaining after infertility treatments should receive timely, relevant, and appropriate information to make informed and voluntary choices regarding disposition of the embryos. Prior to considering the potential research use of the embryos, a prospective donor should have been presented with the option of storing the embryos, donating them to another woman, or discarding them. If a prospective donor chooses to discard embryos remaining after infertility treatment, the option of donating to research may then be presented. (At any point, the prospective donors' questions—including inquiries about possible research use of any embryos remaining after infertility treatment—should be answered truthfully, with all information that is relevant to the questions presented.)

During the presentation about potential research use of embryos that would otherwise be discarded, the person seeking the donation should

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

This proposal also stresses the separation that existing laws and policies seek between the pregnant

woman's decision to abort and her decision to donate cadaveric fetal tissue for transplantation research. Recommendation 1 proposes to extend that separation to the donation of cadaveric fetal tissue for stem cell research. It may be difficult to achieve this separation in making decisions about embryos that remain after infertility treatments, in part because potential donors at the outset of treatment may have chosen to donate them to research. But, however difficult it may be to achieve, this separation will reduce the chance that potential donors could be pressured or coerced into donating their embryos for stem cell research.

The parts of this recommendation that deal with providing information to donors are designed to ensure that potential donors understand the range of available options and that their decisions are not influenced by anticipated personal medical benefits or by concerns about the quality of subsequent care; that they understand that the research will involve the destruction of the embryos; and that they understand the nature of the proposed research, its source of funding, and its anticipated commercial benefits, if known. Several additional suggested information items are proposed in a document entitled "Points to Consider in Evaluating Basic Research Involving Human Embryonic Stem Cells and Embryonic Germ Cells," presented in Appendix F.

Although the ethical considerations that support the prohibition of the designated donation of human fetal tissue are less acute for EG cell research than they are for transplantation, cause for concern remains. Potential donors of cadaveric fetal tissue for EG cell derivation would not have a direct therapeutic incentive to create or abort tissue for research purposes, as might occur in a transplant context. However, we agree that the prohibition remains a prudent and appropriate way to assure that no incentive—however remote—is introduced into a woman's decision to have an abortion. Any suggestion of personal benefit to the donor or to an individual known to the donor would be untenable and potentially coercive. Thus, the potential donor should be informed both before and after the decision to donate that there is no obligation to make such a gift, that no personal benefit will accrue as a result of the decision to donate, and that no penalty or sanction will result from a decision to refuse to donate.

Recommendation 6:

In federally funded research involving embryos remaining after infertility treatments, researchers may not promise donors that ES cells derived from their embryos will be used to treat patient-subjects specified by the donors.

Current provisions regulating fetal tissue research (42 USC § 289g-1 and g-2) have been narrowly interpreted by NIH and DHHS to apply only where fetal cellular material is intended for transfer into a living human recipient for therapeutic or clinical purposes. No comparable rules exist for human embryos. We believe that this statute should be applied more broadly to include *any* research involving human fetal or embryonic tissue, regardless of its immediate or eventual therapeutic benefit or intended method of intervention. Advances in EG cell research have demonstrated that bioethical concerns are not limited to fetal tissue transplantation.

As noted in Chapter 3, the Uniform Anatomical Gift Act (UAGA), currently enacted in some form in all 50 states and the District of Columbia, also may require clarification. Current versions of the UAGA explicitly permit donors to make an anatomical gift of the human body or body parts. Because a fetus is included within the UAGA's definition of *decedent*, either directly or by implication depending upon the statutory language enacted, the statute's anatomical gift provision undermines any federal prohibition of designated donation of human fetal tissue. What would otherwise qualify for federal statutory preemption is clouded by provisions of the NIH Revitalization Act of 1993 and the federal Common Rule, which direct that fetal tissue transplant researchers must abide by local and state laws, including (by implication) the UAGA.

Finally, if and when sufficient scientific evidence becomes available, clinical benefits are clearly anticipated, and agreement is reached among the various elements in society that the creation of embryos specifically for research or therapeutic purposes is justified (specifically through the use of SCNT), prohibitions on directed donation should be revisited. For obvious reasons, the use of SCNT to develop ES cells for autologous transplantation might require that the recipient be specified.

Prohibitions Against the Sale of Embryonic and Fetal Material

Existing rules prohibit the practice of designated donation, the provision of monetary inducements to women undergoing abortion, and the purchase or sale of fetal tissue. We concur in these restrictions and in the recommendation of the 1988 Human Fetal Tissue Transplantation Research Panel that the sale of fetal tissue for research purposes should not be permitted under any circumstances. The potential for coercion is greatest when financial incentives are present, and the treatment of the developing human embryo or fetus as an entity deserving of respect may be greatly undermined by the introduction of any commercial motive into the donation or solicitation of fetal or embryonic tissue for research purposes.

Recommendation 7:

Embryos and cadaveric fetal tissue should not be bought or sold.

Policies already in place state that no for-profit trade in fetal tissue should be permitted, and some recommend that the "prohibition on commercial exchange of fetuses and fetal tissue extend to tissues imported from other countries" (Canadian Royal Commission 1993). This prohibition is intended to prevent the exploitation of poor women—especially those in developing countries—who might be persuaded to begin and end pregnancies for money. An important distinction must be made between the possible exploitation of persons that occurs when they are coerced or inappropriately induced to sell parts of their bodies and the exchanges that occur when companies, research institutions, or other groups provide reasonable compensation. This is a familiar issue in discussions about remuneration for participation in research and about which federal regulations defer to Institutional Review Boards (IRBs) for their judgment.

Current regulations (42 USC §§ 289g-2(a), 289g-2(b)(3), 274e, and 42 CFR § 46.206(b)) attempt to codify this recommendation. Further, depending upon whether a state has enacted the most recent revision of the UAGA (and not all states have enacted the UAGA restriction) and has included the fetus within its definition of *decedent*, the sale of fetal remains may or may not be prohibited by individual state statutes. Many states appear to rely on federal statutes and regulations to prohibit fetal tissue sale, and none address human embryos, except by implication.

We strongly encourage those who will draft modified legislation to frame their language in clear terms that are specifically defined. In particular, terms such as *valuable consideration, processing*, and *reasonable payments* require precise definitions.

We believe that, with respect to these regulations, different categories of research intermediaries should be treated differently. One approach would be to establish three intermediary categories: 1) entities responsible for tissue harvest or embryo collection, 2) entities responsible for stem cell derivation or other preresearch preparation *and* postderivation investigators; and 3) *de minimis* intermediaries (including courier or supply services, off-site specimen evaluation, pathological or chemical analysis for research suitability, and other insignificant non- or preresearch patient or specimen interactions). We believe that the first category warrants the greatest degree of regulation. An abortion provider, IVF clinic, or other third party responsible for obtaining consent and/or collecting biological materials should not be able to commercially solicit, pay for, or be paid for the fetal or embryonic material it obtains (permitting only a specifically defined, cost-based reimbursement exception for entities in that category). By placing such prohibitions against paying those who obtain the embryos, it is our intention to discourage the creation of excess embryos during routine infertility procedures, which would later be used for research purposes.

The National Organ Transplant Act (NOTA) prohibition on tissue sale (42 USC § 274e(a)) has been criticized for a statutory construction that focuses exclusively on the sale of human organs. Although we agree that fetal organ sale (as well as the sale of embryonic material) should be prohibited, we believe that NOTA's terms are unacceptably narrow and that pre-organ tissues characteristic of early fetal and embryonic development should be included in the tissue sale prohibition.

The Need for National Oversight and Review

The need for national oversight and review of ES and EG cell research is crucial. At present, no such system

exists in the United States. A national mechanism to review protocols for deriving human ES and EG cells and to monitor research using such cells would ensure strict adherence to guidelines and standards across the country. Thus, federal oversight can provide the public with the assurance that research involving stem cells is being undertaken appropriately. Given the ethical issues involved in ES and EG cell research—an area in which heightened sensitivity about the very research itself led the President to request that the Commission study the issue—the public and the Congress must be assured that oversight can be accomplished efficiently, constructively, in a timely fashion, and with sufficient attention to the relevant ethical considerations.

Several countries, such as the United Kingdom, have recommended the establishment of regulatory boards or national commissions to license and regulate assisted reproductive treatments and embryo research. The use of a national oversight mechanism of this kind has certain advantages, particularly because the use of law to regulate (rather than to set limits) in this area would be burdensome, given the rapid development of biomedical science and technology. On the other hand, some kind of national commission or authority could provide the necessary flexibility and adaptability, and, in addition, such an entity could ensure more consistent ongoing application of safeguards as well as greater public accountability.[3]

In 1994, the NIH Human Embryo Research Panel considered and then explicitly rejected reconstituting the Ethics Advisory Board (EAB) for the purpose of reviewing proposals involving embryos or fertilized eggs:

> Although revisiting the EAB experience offers the potential for public consensus development and a consistent application of the new guidelines, it nonetheless has significant disadvantages. These include the creation of an additional standing government board, the likelihood of significant delay before embryo research could be funded in order to meet legal requirements for new rulemaking prior to the official creation of the government body, and possible further delay if all proposals for embryo research were required to be considered individually by an EAB-type board, despite appearing to be consistent with a developed consensus at NIH about acceptability for funding (1994, 72).

Instead, the NIH panel recommended that

> national review of all protocols by a diverse group of experts is warranted for a time. It is the hope of the Panel that this ad hoc group will develop additional guidance gained from experience with actual protocols that can be communicated to IRBs through existing mechanisms at NIH (1994, 73).

These recommendations envisioned a time when, following sufficient experience by the ad hoc panel, guidelines for embryo research review could be decentralized to the local IRBs. (It was recommended that the ad hoc panel function for at least three years.) We used similar reasoning in a previous report when recommending that the Secretary of Health and Human Services convene a Special Standing Panel to review certain categories of research involving persons with mental disorders (NBAC 1998). Like the NIH panel, we did not specify when such guidelines could be decentralized; but unlike the NIH panel, we did recommend that the panel be a standing rather than an ad hoc body.

The NIH panel's recommendations must be viewed in the context of its reporting relationship: the panel was charged with advising the NIH Director about research that could be sponsored or conducted by that agency. We note that NIH is not the only federal agency that might be interested in sponsoring or conducting research involving human stem cells; thus, some accommodation must be made for the review of proposals that are not funded by NIH.

Other elements of the NIH panel's recommendation also require additional assessment. For example, the panel recommended that "all such research proposals continue to be specially monitored by the councils and the NIH Office for Protection from Research Risks [OPRR]" (1994, 74). We are less sanguine than the NIH panel about the ability of OPRR to provide the needed oversight and monitoring for ES and EG cell research at this time, particularly given the recent decision to move this office from NIH to DHHS. Although OPRR's role in the oversight of human subjects research, like that of the FDA, remains central to the structure of human subjects protections in this country, we believe that at this time, an additional mechanism is needed for the review and oversight of federally sponsored research involving human ES and EG cells.

We do, however, share the concern of the 1994 NIH panel, investigators, and IRBs that the process of protocol review should not be viewed as simply a bureaucratic hurdle that researchers must successfully leap solely to satisfy a procedural or regulatory requirement. Done well, protocol review often improves the quality of studies by identifying concerns in the areas of study design, selection of subjects, recruitment, informed consent, and dissemination of results.

Recommendation 8:

DHHS should establish a National Stem Cell Oversight and Review Panel to ensure that all federally funded research involving the derivation and/or use of human ES or EG cells is conducted in conformance with the ethical principles and recommendations contained in this report. The panel should have a broad, multidisciplinary membership, including members of the general public, and should

a) **review protocols for the derivation of ES and EG cells and approve those that meet the requirements described in this report,**
b) **certify ES and EG cells lines that result from approved protocols,**
c) **maintain a public registry of approved protocols and certified ES and EG cell lines,**
d) **establish a database—linked to the public registry—consisting of information submitted by federal research sponsors (and, on a voluntary basis, by private sponsors, whose proprietary information shall be appropriately protected) that includes all protocols that derive or use ES or EG cells (including any available data on research outcomes, including published papers),**
e) **use the database and other appropriate sources to track the history and ultimate use of certified cell lines as an aid to policy assessment and formulation,**
f) **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, and**
g) **report at least annually to the DHHS Secretary with an assessment of the current state of the science for both the derivation and use of human ES and EG cells, a review of recent developments in the broad category of stem cell research, a summary of any emerging ethical or social concerns associated with this research, and an analysis of the adequacy and continued appropriateness of the recommendations contained in this report.**

We recommend several functions that the panel should carry out. In order to accomplish its purposes, the panel should maintain a public registry of federally funded protocols that employ or derive human ES and EG cells and, to the degree possible, a comprehensive listing of privately funded protocols. The purpose of the registry is to make it possible to track not only the protocols themselves and their adherence to the principles described above, but also their outcomes and the outcomes of all research based on their results. The panel should be able to describe the history and trajectory of research that uses these cells and to guard against the promiscuous use of the cells. As they are submitted, new federally funded protocols involving the derivation of ES cells must include a statement that only certified cell lines will be used.

Knowledge about the history and ultimate outcome and use of research using human ES and EG cells should be open to the public. Thus, the information accumulated by the panel through the registry should be used not only for ethical review, but also for public education. This is an important educational and informational function that may encourage the active participation of the private sector in the registry—even in the absence of any federal regulatory requirement to do so. In addition, within five years, the panel and the registry should be independently reviewed. This review, which should include an evaluation of the processes of the oversight and review mechanisms, will help to determine whether the level of limitations on this area of research is appropriate as well as to determine whether case-by-case review of derivation protocols is still warranted.

There are several benefits to a national review process for all federally funded research on ES and EG cells. These include preventing ethically problematic research,

assuring the public that the research is scientifically meritorious and ethically acceptable; providing information by which to evaluate issues of social justice in the use of the knowledge or other products of the research; providing public oversight of controversial research practices; assuring consistency in the review of protocols; evaluating this type of research; and educating the public.

Although we are aware that NIH will likely conduct and/or fund the majority of federally sponsored stem cell research in the country and will be developing its own set of guidelines for the conduct of ES and EG cell research, we are persuaded that it is important to distance to some degree the review and oversight of stem cell research from what is the principal source of funding in this country. The proximity of NIH within DHHS (our recommended location for the panel) makes it possible for a number of beneficial arrangements to develop. These include developing requirements for data sharing as a condition for receiving grants; developing guidelines for sharing cell lines; and providing a common review mechanism for other federal agencies that are conducting/funding research involving ES and EG cells (e.g., through a Memorandum of Understanding).

The Need for Local Review of Derivation Protocols

For more than two decades, prospective review by an IRB has been the principal method for assuring that federally sponsored research involving human subjects will be conducted in compliance with guidelines, policies, and regulations designed to protect human beings from harm. This system of local review has been subject to criticism, and, indeed, in previous analyses we have identified a number of concerns regarding this system of review. In preparing this report, we considered a number of proposals that would allow for the local review of research protocols involving human ES and EG cell research, bearing in mind that a decision by the Commission to recommend a role for IRBs might be incorrectly interpreted as endorsing the view that human ES or EG cells or human embryos are human subjects.

We adopted the principle, reflected in these recommendations, that for research involving the derivation of ES and EG cells, a system of national oversight and review would be needed to ensure that important federal sponsorship of stem cell research could proceed—but only under specific conditions. We recognized that for such research proposals, many of the ethical issues could be considered at the local level—that is, at the institutions where the research would be conducted. In general, the IRB is an appropriate body for reviewing protocols that aim to derive ES or EG cells. Although few review bodies (including IRBs) have extensive experience in the review of such protocols, IRBs remain the most visible and expert entities available. It is for this reason, for example, that a number of recommendations presented in this report (8, 9, 10, 11, and 12) discuss the importance of developing additional guidance for the review of protocols that involve human stem cell research.

Recommendation 9:

Protocols involving the *derivation* of human ES and EG cells should be reviewed and approved by an IRB or by another appropriately constituted and convened institutional review body prior to consideration by the National Stem Cell Oversight and Review Panel. (See Recommendation 8.) This review should ensure compliance with any requirements established by the panel, including confirming that individuals or organizations (in the United States or abroad) that supply embryos or cadaveric fetal tissue have obtained them in accordance with the requirements established by the panel.

As noted earlier, for research proposals that involve the derivation of human ES or EG cells, particular ethical issues require attention through a national review process. However, this process should begin at the local level, because institutions that intend to conduct research involving the derivation of human ES cells or EG cells should continue to take responsibility for ensuring the ethical conduct of that research. More important, however, IRBs can play an important role—particularly by reviewing consent documents and by assuring that collaborative research undertaken by investigators at foreign institutions has satisfied any regulatory requirements for the sharing of research materials.

We noted in Chapter 3 that currently there is no definitive answer to the question of whether the

Common Rule, 45 CFR 46, and/or Subpart B apply to research involving fetal tissue transplantation, to human embryo research, and by extension to EG and ES cell research. If the regulations do apply, then IRBs would be expected to review protocols, consistent with the regulatory requirements. We have indicated, however, that even if these regulations do not apply, we believe that IRBs should be expected to review derivation protocols to assess their ethical acceptability without having to commit to a position that the activities are human subjects research as defined by the regulations. If, as a matter of public policy, ES and EG cell research were found to be human subjects research, certain clarifying changes in the regulations might be needed. For example, Subpart B would need to provide clearly that *any* living donor of human biological material constitutes a human subject for purposes of research protection, and IRB review and informed consent under all subparts of the DHHS version of the Common Rule would need to apply. Similarly, we have made clear that the authorization a woman may give to donate fetal tissue following an elective abortion may better be understood as consent to donate—analogous to donating organs—rather than as providing informed consent for research participation. Even if these models differ, the principle we adopt remains the same: opportunity for consent should rest exclusively with the individual or individuals legally empowered to assume a donative role.[4]

Responsibilities of Federal Research Agencies

We have recommended that protocols involving the *derivation* of ES or EG cells should be reviewed by both a local review group and the national panel described in Recommendation 8. For protocols that involve only the use but not the derivation of ES or EG cells, oversight and review are still necessary, but these protocols do not require reliance on such a system. In our judgment, these protocols can be appropriately reviewed using the existing system for the submission, review, and approval of research proposals that is in place at federal research agencies, which includes the use of a peer review group—sometimes called a study section or initial review group—that is established to assess the scientific merit of the proposals. In addition, in some agencies, such as NIH, staff members review protocols before they are transmitted to a national advisory council for final approval. These levels of review all provide an opportunity to consider ethical issues that arise in the proposals. When research proposals involve human subjects, in order to assure that it is ethically acceptable, federal agencies rely on local IRBs for review and approval. (See Recommendation 9.) At every point in this continuum—from the first discussions that a prospective applicant may have with program staff within a particular institute to the final decision by the relevant national advisory council—ethical and scientific issues can be addressed by the sponsoring agency. But even if—based on a particular interpretation of the federal regulation—these research proposals do not involve human subjects, we believe the system of oversight and review can adequately address the relevant ethical issues.

Recommendation 10:

All federal agencies should ensure that their review processes for protocols using human ES or EG cells comply with any requirements established by the National Stem Cell Oversight and Review Panel (see Recommendation 8), paying particular attention to the adequacy of the justification for using such cell lines.

Research involving human ES and EG cells raises critical ethical issues, particularly when the proposals involve the derivation of ES cells from embryos that remain after infertility treatments. We recognize that these research proposals may not follow the paradigm that is usually associated with human subjects research. Nevertheless, research proposals that are being considered for funding by federal agencies must, in our view, meet the highest standards of scientific merit and ethical acceptability. To that end, the recommendations made in this report, including a proposed set of points to consider in evaluating basic research involving human ES cells and EG cells (see Appendix F), constitute a set of ethical and policy considerations that should be reflected in the respective policies of federal agencies conducting or sponsoring human ES or EG cell research.

Attention to Issues for the Private Sector

Although this report primarily addresses the ethical issues associated with the use of federal funds for research involving the derivation and/or use of ES and

EG cells, we recognize that considerable work in both of these areas will be conducted under private sponsorship. Thus, our recommendations may have implications for those working in the private sector. First, for cell lines to be eligible for use in federally funded research, they must be certified by the National Stem Cell Oversight and Review Panel described in Recommendation 8. Therefore, if a private company aims to make its cell lines available to publicly funded researchers, it must submit its derivation protocol(s) to the same oversight and review process recommended for the public sector, (i.e., local review; see Recommendation 9) and for certification by the proposed national panel that the cells have been derived from embryos remaining after infertility treatments or from cadaveric fetal tissue.

Second, we hope that nonproprietary aspects of protocols developed under private sponsorship will be made available in the public registry, as described in Recommendation 8. The greater the participation of the private sector in providing information on human ES and EG cell research, the more comprehensive the development of the science and related public policies in this area.

Third, and perhaps most relevant in an ethically sensitive area of emerging biomedical research, it is important that all members of the research community, whether in the public or private sector, conduct the research in a manner that is open to appropriate public scrutiny. During the last two decades, we have witnessed an unprecedented level of cooperation between the public and private sectors in biomedical research, which has resulted in the international leadership position of the United States in this area. Public bodies and other authorities, such as the Recombinant DNA Advisory Committee, have played a crucial role in enabling important medical advances in fields such as gene therapy by providing oversight of both publicly and privately funded research efforts. We believe that voluntary participation by the private sector in the review and certification procedures of the proposed national panel, as well as in its deliberations, can contribute equally to the socially responsible development of ES and EG cell technologies and accelerate their translation into biomedically important therapies that will benefit patients.

Recommendation 11:

For privately funded research projects that involve ES or EG cells that would be eligible for federal funding, private sponsors and researchers are encouraged to adopt voluntarily the applicable recommendations of this report. This includes submitting protocols for the derivation of ES or EG cells to the National Stem Cell Oversight and Review Panel for review and cell line certification. (See Recommendations 8 and 9.)

In this report, we recommend that federally funded research that involves the derivation of ES cells should be limited to those efforts that use embryos that remain after infertility treatments. Some of the recommendations made in this context—such as the requirement for separating the decision by a woman to cease infertility treatment when embryos still remain from her decision to donate those embryos to research—simply do not apply to efforts to derive ES cells from embryos created (whether by IVF or by SCNT) solely for research purposes—activities that might be pursued in the private sector. Nevertheless, other ethical standards and safeguards embodied in the recommendations, such as provisions to prevent the coercion of women and the promotion of commerce in human reproduction, remain vitally important, even when embryos are created solely for research purposes.

Recommendation 12:

For privately funded research projects that involve deriving ES cells from embryos created solely for research purposes and that are therefore not eligible for federal funding (see Recommendations 3 and 4)

a) professional societies and trade associations should develop and promulgate ethical safeguards and standards consistent with the principles underlying this report, and

b) private sponsors and researchers involved in such research should voluntarily comply with these safeguards and standards.

Professional societies and trade associations dedicated to reproductive medicine and technology play a central role in establishing policy and standards for clinical care, research, and education. We believe that these organizations

can and should play a salutary role in ensuring that all embryo research conducted in the United States, including that which is privately funded, conforms to the ethical principles underlying this report. Many of these organizations already have developed policy statements, ethics guidelines, or other directives addressing issues in this report, and we have benefited from a careful review of these materials. These organizations are encouraged to review their professional standards to ensure not only that they keep pace with the evolving science of human ES and EG cell research, but also that their members are knowledgeable about and in compliance with them. For those organizations that conduct research in this area but that lack statements or guidelines addressing the topics of this report, we recommend strongly that they develop such statements or guidelines. No single institution or organization, whether in the public or the private sector, can provide all the necessary protections and safeguards.

The Need for Ongoing Review and Assessment

No system of federal oversight and review of such a sensitive and important area of investigation should be established without at the same time providing an evaluation of its effectiveness, value, and ongoing need. The pace of scientific development in human ES and EG cell research likely will increase. Although one cannot predict the direction of the science of human stem cell research, in order for the American public to realize the promise of this research and to be assured that it is being conducted responsibly, close attention to and monitoring of all the mechanisms established for oversight and review are required.

Recommendation 13:

The National Stem Cell Oversight and Review Panel described in Recommendation 8 should be chartered for a fixed period of time, not to exceed five years. Prior to the expiration of this period, DHHS should commission an independent evaluation of the panel's activities to determine whether it has adequately fulfilled its functions and whether it should be continued.

There are several reasons for allowing the national panel to function for a fixed period of time and for evaluating its activities before it continues its work. First, some of the hoped-for results will be available from research projects that are using the two sources we consider to be ethically acceptable for federal funding. Five years is a reasonable period in which to allow some of this information to amass, offering the panel, researchers, members of Congress, and the public sufficient time to determine whether any of the knowledge or potential health benefits are being realized. The growing body of information in the public registry and database described above (particularly if privately funded researchers and sponsors voluntarily participate) will aid these considerations.

Second, within this period the panel may be able to determine whether additional sources of ES cells are necessary in order for important research to continue. Two arguments have been offered for supporting research using embryos created specifically for research purposes: One is the concern that not enough embryos remain for this purpose from infertility treatments, and the other is the recognition that some research requires embryos that are generated for specific research and/or medical purposes. The panel should assess whether additional sources of ES cells that we have judged to be ineligible for federal funding at this time (i.e., embryos created solely for research purposes) are legitimately needed.

Third, an opportunity to assess the relationship between local review of protocols using human ES and EG cells and the panel's review of protocols for the derivation of ES cells will be offered. It will, of course, take time for this national oversight and review mechanism to develop experience with the processes of review, certification, and approval described in this report.

Fourth, we hope that the panel will contribute to the broad and ongoing national dialogue on the ethical issues regarding research involving human embryos. A recurring theme of our deliberations, and in the testimony we heard, was the importance of encouraging this national conversation.

The criteria for determining whether the panel has adequately fulfilled its functions should be set forth by an independent body established by DHHS. However, it would be reasonable to expect that the evaluation would rely generally on the seven functions described above in Recommendation 8 and that this evaluation would be conducted by a group with the requisite expertise. In

addition, some of the following questions might be considered when conducting this evaluation: Is there reason to believe that the private sector is voluntarily submitting descriptions of protocols involving the derivation of human ES cells to the panel for review? Is the panel reviewing projects in a timely manner? Do researchers find that the review process is substantively helpful? Is the public being provided with the assurance that social and ethical issues are being considered?

Summary

Recent developments in human ES and EG cell research have raised the prospect that new therapies will become available that will serve to relieve human suffering. These developments also have served to remind society of the deep moral concerns that are related to research involving human embryos and cadaveric fetal tissue. Serious ethical discussion will (and should) continue on these issues. However, in light of public testimony, expert advice, and published writings, we have found substantial agreement among individuals with diverse perspectives that although the human embryo and fetus deserve respect as forms of human life, the scientific and clinical benefits of stem cell research should not be foregone. We were persuaded that carrying out human ES cell research under federal sponsorship is important, but only if it is conducted in an ethically responsible manner. After extensive deliberation, the Commission believes that acceptable public policy can be forged, in part, based upon these widely shared views. Through this report, we not only offer recommendations regarding federal funding and oversight of stem cell research, but also hope to further stimulate the important public debate about the profound ethical issues regarding this potentially beneficial research.

Notes

1 Use of fetal tissue in research is also permitted in Canada, the United Kingdom, Australia, and in most countries in the European Union. Germany, for example, does not permit embryo research but does permit the use of fetal tissue for the derivation of EG cells. The German statement concerning human ES cells upholds the ban on destructive embryo research, effectively banning the derivation of ES cells, because the option of deriving EG cells exists in that country. See the German statement concerning the question of human ES cells, March 1999, 8–10 (DFG 1999).

2 Public Law No. 105-78, 513(a) (1997).

3 EGE *Opinion* (1998) at Art. 2.11. See also the Australian NHMRC *Guidelines* (1996) advocating that complementary national assisted reproductive technology standards or legislation be adopted in the Australian States.

4 See *Fed. Reg.* 27804, proposed rule 45 CFR § 46.204(d)-(e) and Table 1, "Current and Proposed 45 CFR 46, Subpart B," 27798, explanatory text ("consent of the father is not required"; rather, "consent of the mother *or* her legally authorized representative is required" [after she is]..."informed of the reasonably foreseeable impact of the research on the fetus").

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Appendix A

Acknowledgments

This report benefited from the input of many individuals and groups. Several organizations responded to a February 1999 request from the National Bioethics Advisory Commission for input on the scientific, medical, and ethical issues involved in human stem cell research, and nearly 40 scientific, medical, professional, religious, and health organizations were asked to provide their perspectives on these complex issues. The Commission gratefully acknowledges the thoughtful comments provided by the following groups:

- American Bioethics Advisory Commission (Stafford, Virginia)
- The American College of Obstetricians and Gynecologists (Washington, DC)
- The American Society for Cell Biology (Bethesda, Maryland)
- American Society for Reproductive Medicine (Birmingham, Alabama)
- Association of American Medical Colleges (Washington, DC)
- Biotechnology Industry Association (Washington, DC)
- College of American Pathologists (Northfield, Illinois)
- Pharmaceutical Research and Manufacturers of America (Washington, DC)
- RESOLVE (Somerville, Massachusetts)

In addition, the Commission asked the following individuals to review portions of the draft report for scientific, legal, and ethical accuracy. The comments provided by these individuals improved the quality and outcome of the report and are greatly appreciated:

- Brigid L.M. Hogan (Vanderbilt University School of Medicine; Nashville, Tennessee)
- Anna Mastroianni (University of Washington; Seattle, Washington)
- John A. Robertson (The University of Texas; Austin, Texas)
- Janet Rossant (Samuel Lunenfeld Research Institute, Mt. Sinai Hospital; Toronto, Ontario)
- Lee Silver (Princeton University; Princeton, New Jersey)
- Evan Y. Snyder (Harvard Medical School; Cambridge, Massachusetts)
- James A. Thomson (University of Wisconsin; Madison, Wisconsin)

We are also grateful to Michelle Myer, a graduate student at the University of Virginia, for preparing a summary of the presentations that were provided to the Commission on May 7, 1999, on religious perspectives relating to research involving human stem cells. The summary appears as Appendix E of this report.

Appendix B

Glossary

adult stem (AS) cells – stem cells found in the adult organism (e.g., in bone marrow, skin, and intestine) that replenish tissues in which cells often have limited life spans. They are more differentiated than embryonic stem (ES) cells or embryonic germ (EG) cells.

ART (assisted reproductive technology) – all treatments or procedures that involve the handling of human eggs and sperm for the purpose of helping a woman become pregnant. Types of ART include *in vitro* fertilization, gamete intrafallopian transfer, zygote intrafallopian transfer, embryo cryopreservation, egg or embryo donation, and surrogate birth.

blastocyst – a mammalian embryo in the stage of development that follows the morula. It consists of an outer layer of trophoblast to which is attached an inner cell mass.

blastomere – one of the cells into which the egg divides after its fertilization; one of the cells resulting from the division of a fertilized ovum.

chimera – an organism composed of two genetically distinct types of cells.

cloning – the production of a precise genetic copy of a molecule (including DNA), cell, tissue, plant, or animal.

differentiation – the specialization of characteristics or functions of cell types.

diploid cell – the cell containing two complete sets of genes derived from the father and the mother respectively; the normal chromosome complement of somatic cells (in humans, 46 chromosomes).

ectoderm – the outer layer of cells in the embryo; the origin of skin, the pituitary gland, mammary glands, and all parts of the nervous system.

embryo – 1) the beginning of any organism in the early stages of development, 2) a stage (between the ovum and the fetus) in the prenatal development of a mammal, 3) in humans, the stage of development between the second and eighth weeks following fertilization, inclusive.

embryonic stem (ES) cells – cells that are derived from the inner cell mass of a blastocyst embryo.

embryonic germ (EG) cells – cells that are derived from precursors of germ cells from a fetus.

endoderm – the innermost of the three primary layers of the embryo; the origin of the digestive tract, the liver, the pancreas, and the lining of the lungs.

ex utero – outside of the uterus.

fibroblast – a cell present in connective tissue, capable of forming collagen fibers.

gamete – 1) any germ cell, whether ovum or spermatozoon, 2) a mature male or female reproductive cell.

gastrulation – the process of transformation of the blastula into the gastrula, at which point the embryonic germ layers or structures begin to be laid out.

germ cells – gametes (ova and sperm) or the cells that give rise directly to gametes.

haploid cell – a cell with half the number of chromosomes as the somatic diploid cell, such as the ova or sperm. In humans, the haploid cell contains 23 chromosomes.

in vivo – in the natural environment (i.e., within the body).

in vitro – in an artificial environment, such as a test tube or culture medium.

***in vitro* fertilization (IVF)** – a process by which a woman's eggs are extracted and fertilized in the laboratory and then transferred after they reach the embryonic stage into the woman's uterus through the cervix. Roughly 70 percent of assisted reproduction attempts involve IVF, using fresh embryos developed from a woman's own eggs.

karyotype – the chromosome characteristics of an individual cell or of a cell line, usually presented as a systematic array of metaphase chromosomes from a photograph of a single cell nucleus arranged in pairs in descending order of size.

mesoderm – the middle of the three primary germ layers of the embryo; the origin of all connective tissues, all body musculature, blood, cardiovascular and lymphatic systems, most of the urogenital system, and the lining of the pericardial, pleural, and peritoneal cavities.

morula – 1) the mass of blastomeres resulting from the early cleavage divisions of the zygote, 2) solid mass of cells resembling a mulberry, resulting from the cleavage of an ovum.

oocyte – 1) a diploid cell that will undergo meiosis (a type of cell division of germ cells) to form an egg, 2) an immature ovum.

ovum – female reproductive or germ cell.

pluripotent cells – cells, present in the early stages of embryo development, that can generate all of the cell types in a fetus and in the adult and that are capable of self-renewal. Pluripotent cells are not capable of developing into an entire organism.

pre-implantation embryo – 1) the embryo before it has implanted in the uterus, 2) commonly used to refer to *in vitro* fertilized embryos before they are transferred to a woman's uterus.

somatic cells – [from *soma* - the body] 1) cells of the body which in mammals and flowering plants normally are made up of two sets of chromosomes, one derived from each parent, 2) all cells of an organism with the exception of germ cells.

stem cells – cells that have the ability to divide indefinitely and to give rise to specialized cells as well as to new stem cells with identical potential.

totipotent – having unlimited capacity. Totipotent cells have the capacity to differentiate into the embryo and into extra-embryonic membranes and tissues. Totipotent cells contribute to every cell type of the adult organism.

trophoblast – the outermost layer of the developing blastocyst of a mammal. It differentiates into two layers, the cytotrophoblast and syntrophoblast, the latter coming into intimate relationship with the uterine endometrium with which it establishes nutrient relationships.

zygote – 1) the cell resulting from the fusion of two gametes in sexual reproduction, 2) a fertilized egg (ovum), 3) the diploid cell resulting from the union of a sperm and an ovum, 4) the developing organism during the first week after fertilization.

Appendix C

Letters of Request and Response

THE WHITE HOUSE

WASHINGTON

November 14, 1998

Dr. Harold Shapiro
Chair
National Bioethics Advisory Commission
Suite 3C01
6100 Executive Boulevard
Bethesda, Maryland 20892-7508

Dear Dr. Shapiro:

This week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious of ethical, medical, and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species. I am therefore requesting that the National Bioethics Advisory Commission consider the implications of such research at your meeting next week, and to report back to me as soon as possible.

I recognize, however, that other kinds of stem cell research raise different ethical issues, while promising significant medical benefits. Four years ago, I issued a ban on the use of federal funds to create human embryos solely for research purposes; the ban was later broadened by Congress to prohibit any embryo research in the public sector. At that time, the benefits of human stem cell research were hypothetical, while the ethical concerns were immediate. Although the ethical issues have not diminished, it now appears that this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes, and Parkinson's disease. With this in mind, I am also requesting that the Commission undertake a thorough review of the issues associated with such human stem cell research, balancing all ethical and medical considerations.

I look forward to receiving your reports on these important issues.

Sincerely,

Bill Clinton

NATIONAL BIOETHICS ADVISORY COMMISSION

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November 20, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg.

The Commission shares your view that this development raises important ethical and potentially controversial issues that need to be considered, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

We devoted time at our meeting to discussing various aspects of this issue, benefiting not only from the expertise of the Commissioners, but from our consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members. As you know, however, the design and results of this experiment are not yet publicly available, and as a consequence the Commission was unable to evaluate fully its implications.

As a framework for our initial discussion, we found it helpful to consider three questions:

1. ***Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?***

At this time, there is insufficient scientific evidence to answer this question. What little evidence exists, based on other fusions of non-human eggs with non-human cells from a different species, suggests that a pregnancy cannot be maintained. If it were possible, however, for a child to develop from these fused cells, then profound ethical issues would be raised. An attempt to develop a child from these fused cells should not be permitted.

This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

> "...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning."

2. Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?

The common understanding of a human embryo includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living human being. At this time, however, there is insufficient scientific evidence to be able to say whether the combining of a human cell and the egg of a non-human animal results in an embryo in this sense. In our opinion, if this combination does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these hybrid cells will contain both human and non-human biological material.

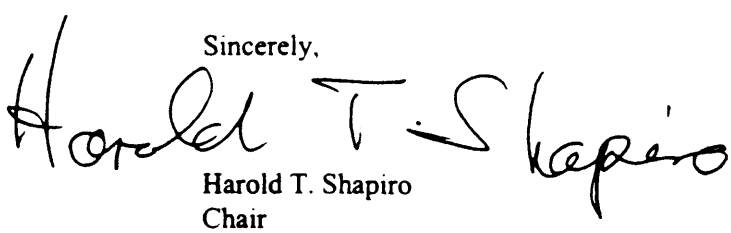
It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Human embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of human embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

3. If the fusion of a human cell and the egg of a non-human animal does not result in an embryo with the potential to develop into a child, what ethical issues remain?

If this line of research does not give rise to human embryos, we do not believe that totally new ethical issues arise. We note that scientists routinely conduct non-controversial and highly beneficial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,



Harold T. Shapiro
Chair

Appendix D

The Food and Drug Administration's Statutory and Regulatory Authority to Regulate Human Stem Cells[1]

An Overview of Food and Drug Administration Regulations Pertinent to Human Cellular Materials and Tissues

The Food and Drug Administration (FDA) has had in place a regulatory framework for cellular and tissue materials that has evolved over time as the development and use of such biological materials for therapeutic purposes has increased. The Public Health Service Act (PHS Act), 42 USC 262 and 264, the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 USC 201 et seq., and implementing regulations of the FDA provide the agency with broad authority to regulate both the research into and the use of human stem cells that are *intended to be used as* biological products, drugs, or medical devices in order to prevent, treat, cure, or diagnose a disease or condition.[2] Scientific research not intended for use in the development of any FDA-regulated product is not under the oversight and control of the FDA.

In order for the FDA to assert its regulatory authority over stem cell-related research and products, such research *and* products must fall within one of the product categories over which the FDA exercises jurisdiction and must move in interstate commerce. To the extent that the FDA determines that a particular product falls within the definition of a biological product, a drug, or a medical device, it will assert its jurisdiction. Whether a particular product falls within the definition of any of the FDA-regulated product categories will depend, in part, upon the intended use of the product.

The manufacturer's objective intent—as evidenced by labeling, promotional, and other relevant materials for the product—has long been regarded as the primary source for establishing a product's intended use and thus its status for purposes of FDA regulation.[3] Although this approach would seem to grant manufacturers unlimited control over the regulatory status of their products, courts in fact have recognized the FDA's right to look beyond the express claims of manufacturers in order to consider more subjective indicia of intent—such as the foreseeable and actual use of a product—to prove that its intended use subjects it to agency jurisdiction.[4]

Regardless of whether the FDA or the manufacturer is characterizing the intended use of a product for purposes of evaluating FDA jurisdiction, it is clear that FDA regulatory authority will not extend automatically to all scientific research on stem cells. Indeed, to the extent that such nonhuman research is preliminary in nature and/or is undertaken without intent to develop a therapeutic product, stem cell research is not subject to FDA jurisdiction. Thus, for example, basic research to develop stem cell models to evaluate the safety and efficacy of therapeutic products would not be regulated directly. Instead, the FDA would review any scientific data generated from such a model and submitted as part of a marketing application. It is only at the juncture when the science of stem cell research has progressed to the point that development of a particular therapeutic product and its use in humans is envisioned that FDA regulatory authority will apply, and further research then must be conducted in compliance with FDA requirements.

Even if a product falls within one of the defined categories over which the FDA asserts its jurisdiction, no

statutory authority over the product exists unless it moves in interstate commerce. The FDA takes an expansive view of what constitutes interstate commerce; in regard to biological products, the FDA has been particularly aggressive. For example, in its 1993 policy statement regarding somatic cell therapy products, the FDA concluded that

> [t]he interstate commerce nexus needed to require premarket approval under the statutory provisions governing biological products and drugs may be created in various ways in addition to shipment of the finished product by the manufacturer. For example, even if a biological drug product is manufactured entirely with materials that have not crossed State lines, transport of the product into another State by an individual patient creates the interstate commerce nexus. If a component used in the manufacture of the product moves interstate, the interstate commerce prerequisite for the prohibition against drug misbranding is also satisfied even when the finished product stays within the State. Products that do not carry labeling approved in a PLA (or NDA) are misbranded under section 502(f)(1) of the [FD&C] Act....Moreover, falsely labeling a biological product is prohibited under section 351(b) of the PHS Act without regard to any interstate commerce nexus (42 U.S.C. 262(b)) (58 *Fed. Reg.* at 53250).

It can be expected that the FDA would apply the same logic to all cellular and tissue materials that are used in the prevention, treatment, cure, or diagnosis of a disease or condition.

Application to Stem Cells

In recent congressional testimony, National Institutes of Health Director Harold Varmus described three potential applications of research using human "pluripotent stem cells" that illustrate the inconsistencies of FDA regulation. He noted that the FDA does not regulate two of the examples, but will regulate one. First, stem cell research could include basic research such as "the identification of the factors involved in the cellular decision-making process that determines cell specialization."[5] Second, "[h]uman pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease process."[6] It is unlikely that the FDA would regulate either of these potential applications directly. Varmus also made the following comments:

> Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burn, heart disease, diabetes, osteoarthritis and rheumatoid arthritis.[7]

These stem cell products, based on their *intended use*, would be subject to FDA regulation.

Case-by-Case Regulation

The FDA has been cautious in exercising its regulatory discretion regarding cellular and tissue materials and in fact never has overseen a single regulatory program for human cellular and tissue-based products. Instead, the FDA has regulated these products on a case-by-case basis, responding as it deemed appropriate to the particular characteristics of and concerns raised by each type of product.[8]

One example has been the FDA's approach to regulating bone marrow. Although for years the FDA has licensed blood and blood components pursuant to section 351 of the PHS Act (42 USC 262), it voluntarily has refrained from regulating minimally manipulated bone marrow, the earliest source of stem cells used for transplantation, despite its status as a blood component. Indeed, not until the early 1990s did the FDA announce that to the extent that bone marrow was subject to extensive manipulation prior to transplantation, it would be treated the same as somatic cell therapy and gene therapy products subject to the investigational new drug (IND) regulations and would require PHS Act licensure (58 *Fed. Reg.* 53248, 53249 (Oct. 14, 1993)).

Also in 1993, in response to concerns regarding the transmission of the human immunodeficiency virus (HIV) and other infectious diseases, the FDA published an

emergency final rule that mandated certain processing, testing, and recordkeeping procedures for specific types of tissue products.[9] This rule, however, did *not* mandate premarket approval or notification for all tissues, but rather provided, among other things, for donor screening, documentation of testing, and FDA inspection of tissue facilities.[10]

Another example of the FDA's case-by-case approach is the publication in 1996 of a guidance that stated that manipulated autologous structural cells (autologous cells manipulated and then returned to the body for structural repair or reconstruction) would be subject to PHS licensure.[11] In addition, until recently, the FDA carefully chose not to regulate reproductive tissues. Then, in 1997, it proposed that, in the future, certain reproductive tissues (i.e., semen, ova, and embryos) should be regulated in some form.

Traditional tissue products (including but not limited to bone, skin, corneas, and tendons) also have been subject to the FDA's piecemeal regulatory approach. Historically, the FDA regulated these products on an ad hoc basis as medical devices under section 201 of the FD&C Act. However, with the advent of HIV and the potential for its transmission, the FDA concluded in the early 1990s that a more comprehensive program for regulating the use of traditional tissues was necessary. In 1991, the FDA concluded that human heart valves were medical devices subject to premarket approval requirements.[12] Following litigation, the FDA decided that while these products were indeed medical devices, they would not be subject to premarket approval requirements.[13] In defining tissue subject to this rule, the FDA exempted a number of products, including vascularized organs, *dura mater*, allografts, and umbilical cord vein grafts.

A New Approach to Regulating Human Cellular and Tissue-Based Products

In February 1997 the FDA proposed a new approach to the regulation of human cellular and tissue-based products. This framework is intended to "protect the public health without imposing unnecessary government oversight" ("Reinventing the Regulation of Human Tissue," *National Performance Review*, February 1997). Although it is still considered a proposed approach, the 1997 document utilizes FDA's existing statutory authority under the PHS and FD&C Acts to regulate a broad array of cellular and tissue materials. The framework proposed is a tiered approach to regulation (FDA, "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products," February 28, 1997). Products that pose increased risks to health or safety would be subject to increased levels of regulation (i.e., either licensure under the PHS Act or premarket approval under the FD&C Act), while products that pose little or no risk of transmitting infectious disease would be subject to minimal regulation (e.g., facility registration and product listing). However, products that are 1) highly processed (more-than-minimally manipulated); 2) are used for other than their usual purpose; 3) are combined with nontissue components (e.g., devices or other therapeutic products); or 4) are used for metabolic purposes (e.g., systemic, therapeutic purposes) will be subject to clinical investigation as INDs, must be documented with investigational device exemption applications (IDEs), and will be subject to premarket approval as biological products, medical devices, or new drugs.

This proposed approach addresses the FDA's regulation of stem cell products. In the case of a minimally manipulated product for autologous use and allogeneic use of cord blood stem cells by a close blood relative, the FDA has proposed requiring compliance with standards consistent with section 361 of the PHS Act, rather than an IND and licensure pursuant to section 351 of the act. However, minimally manipulated products that will be used by an unrelated party will be regulated under section 351 of the Act. The FDA also intends to develop standards—including disease screening requirements, establishment controls, processing controls, and product standards: "If sufficient data are not available to develop processing and product standards after a specified period of time, the stem cell products would be subject to IND and marketing application requirements."[14] Stem cell products that are more-than-minimally manipulated will require INDs and licensing under section 351 of the PHS Act. For example, stem cell products that are to be used for a nonhomologous function or are more-than-minimally manipulated will be required to be licensed under

section 351. The FDA also has articulated "increased safety and effectiveness concerns for cellular and tissue-based products that are used for nonhomologous function, because there is less basis on which to predict the product's behavior."[15]

Implementation of the Proposed Approach

The FDA has begun to implement the proposed approach with the publication on January 20, 1998, of a *Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products*" (63 *Fed. Reg.* 2985), utilizing its standards-setting authority under section 361 of the PHS Act.[16] In this notice, the FDA requests product standards to ensure the safety and effectiveness of stem cell products, which should be supported by clinical and nonclinical laboratory data. The FDA also announced its intention to phase in over a three-year period implementation of IND application and license application requirements for minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products. The notice states that "[i]f adequate information can be developed, the agency intends to issue guidance for establishment controls, processing controls, and product standards....FDA intends to propose that, in lieu of individual applications containing clinical data, licensure may be granted for products certified as meeting issued standards." If, however, the FDA determines that adequate standards cannot be developed, the agency has expressed its intention to enforce IND and licensing requirements at the end of three years. Proposals are due on or before January 20, 2000.

On May 14, 1998, the FDA proposed *Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products* (63 *Fed. Reg.* 26744). The agency describes the proposed registration and listing requirements as a first step towards accomplishing its goal of putting into place a comprehensive new system of regulation for human cellular and tissue-based products. Registration and listing is intended to allow the FDA to assess the state of the cell and tissue industry, "to accrue basic knowledge about the industry that is necessary for its effective regulation," and to facilitate communication between the agency and industry (Ibid. at 26746). As proposed, the registration and listing requirements would apply to human cellular and tissue-based products that the FDA will regulate under section 361 of the PHS Act.[17] Among the products designated for regulation under that section and consequently subject to registration and listing are bone, tendons, skin, corneas, as well as peripheral and cord blood stem cells under certain conditions, and sperm, oocytes, and embryos for reproductive use (Ibid. at 26746).

FDA Discretion Entitled to Great Deference

Today there is a vast array of biological products that have been approved by the FDA and many others that are awaiting FDA action.[18] These products are scientifically complex and rarely lend themselves to categorization. As a result, the FDA invariably is required to determine on a case-by-case basis whether its existing statutory authority applies to a new product, which particular authority to apply, and, if so, what evidence will adequately demonstrate proof of safety, purity, and potency (efficacy). The decision of whether and how to regulate a product is made based upon the FDA's expert determination and upon the particular facts and circumstances, the historical application of the law to similar products, the applicable statutory and regulatory criteria, and the state of the FDA's scientific understanding at the time of the approval.

The FDA's exercise of the significant discretion provided to the agency by Congress is entitled to great deference by the courts.[19] In a recent challenge to the FDA's approval of a biological product under the PHS Act, the District Court for the District of Columbia held that "FDA's policies and its interpretation of its own regulations will be paid special deference *because of the breadth of the Congress' delegation of authority to FDA and because of FDA's scientific expertise.*"[20]

Moreover, even if the FDA has not asserted jurisdiction previously with regard to reproductive tissue, for example, it is within the agency's statutory authority that its policies are evolutionary. The Supreme Court has recognized that expert administrative agency interpretations are not "carved in stone. On the contrary, the

agency...must consider varying interpretations and the wisdom of its policy *on a continuing basis*" (emphasis added).[21] Furthermore, the Court has acknowledged that "regulatory agencies do not establish rules of conduct to last forever....[A]n agency must be given ample latitude to 'adapt their rules and policies to the demands of changing circumstances.'"[22]

Conclusion

The FDA has developed a comprehensive approach to the regulation of cellular and tissue-based therapeutic products under its jurisdiction, including human stem cells. Nonclinical and clinical stem cell research undertaken to develop a therapeutic product intended to treat human disease will continue to be regulated by the FDA, while basic scientific research and other nonhuman research will remain outside of the agency's purview.

Notes

1 The content of this appendix is based upon a paper commissioned by the National Bioethics Advisory Commission and prepared by Brady, R.P., M.S. Newberry, and V.W. Girard, "The Food and Drug Administration's Statutory and Regulatory Authority to Regulate Human Pluripotent Stem Cells," available in Volume II of this report.

2 The scope of this appendix is limited to human stem cells. The FDA has a similar regulatory structure to regulate animal stem cell products used as animal drugs (21 USC 360b). The U.S. Department of Agriculture has the authority to regulate animal stem cell products used in animal vaccines (21 USC 151).

3 See *United States v. An Article...Sudden Change*, 409 F.2d 734, 739 (2d Cir. 1969).

4 See *National Nutritional Foods Ass'n. v. Mathews*, 557 F.2d. 325, 334 (2d Cir. 1977); *Action on Smoking and Health v. Harris*, 655 F.2d 236, 240–41 (D.C. Cir. 1980).

5 Statement of Harold Varmus, M.D., Director, National Institutes of Health, before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies. December 2, 1998. Meeting transcript, 3.

6 Ibid.

7 Ibid. 3–4.

8 63 *Fed. Reg.* 26744 (May 14, 1998) (FDA Proposed Rule "Establishment and Listing for Manufacturers of Human Cellular and Tissue-Based Products").

9 "Human Tissue Intended for Transplantation" 58 *Fed. Reg.* 65514 (Dec. 14, 1993).

10 In 1997, FDA finalized its 1993 emergency rule establishing processing, testing, and recordkeeping requirements for all tissue products. "Human Tissue Intended for Transplantation" 62 *Fed. Reg.* 40429 (July 29, 1997).

11 CBER, Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated *Ex Vivo* and Intended for Structural Repair or Reconstruction (May 1996).

12 "Cardiovascular Devices; Effective Date of Requirement for Premarket Approval; Replacement Heart Valve Allograft" 56 *Fed. Reg.* 29177 (June 26, 1991).

13 FDA Rescission Notice, 59 *Fed. Reg.* 52078 (October 14, 1994).

14 Proposed Approach, 25.

15 Proposed Approach, 16.

16 While FDA may choose to implement this policy through regulation, FDA also may implement it on a case-by-case basis. See infra, Section VI.

17 Consistent with the discussion supra, Section III. A., the preamble to the proposed rule states that "use of human cellular or tissue-based products solely for nonclinical scientific or educational purposes does not trigger the registration or listing requirements. Any use for implantation, transplantation, infusion, or transfer into humans is considered clinical use and would be subject to part 1271 [the registration and listing requirements]" Ibid. 26748.

18 Today, biological products are available or under development to treat, diagnose, or prevent virtually every serious or life-threatening disease. Available products include, but are not limited to, vaccines (manufactured both in traditional ways and through the use of biotechnology); human blood and blood-derived products; monoclonal or polyclonal immunoglobulin products; human cellular (i.e., gene therapy) products; protein, peptide, and carbohydrate products; protein products produced in animal body fluids by genetic alteration of the animal (i.e., transgenic animals); animal venoms; and allergenic products.

19 *U.S. v. Rutherford*, 442 U.S. 544, 553 (1979); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996).

20 *Berlex Laboratories, Inc. v. FDA* et al., 942 F. Supp. 19 (D.D.C. 1996) (emphasis added). See also *Lyng v. Payne*, 476 U.S. 926 (1986).

21 *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 863–64 (1984).

22 *Motor Vehicle Mfrs. Ass'n. of the U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983) (citations omitted).

Appendix E

Summary of Presentations on Religious Perspectives Relating to Research Involving Human Stem Cells, May 7, 1999

Introduction

As part of the National Bioethics Advisory Commission's deliberations for this report, a meeting was convened on May 7, 1999, at Georgetown University in order for the Commission to hear testimony from prominent scholars of religious ethics on their traditions' views of human stem cell research. Although it would be inappropriate for religious views to determine public policy in our country, such views are the products of long traditions of ethical reflection, and they often overlap with secular views. Thus, the Commission believed that testimony from scholars of religious ethics was crucial to its goal of informing itself about the range, content, and rationale of various ethical positions regarding research in this area.

The Commission heard testimony from scholars who work within the Roman Catholic, Protestant, Eastern Orthodox, Jewish, and Islamic faiths. Although the presenters were able to reach consensus on several significant issues related to embryonic stem (ES) and embryonic germ (EG) cell research, disagreement emerged among the religious traditions represented and often within each tradition itself, particularly between restrictive and permissive positions on several issues.

Roman Catholic Perspectives

The restrictive, "official" position within Roman Catholicism opposes EG and ES cell research, primarily because obtaining stem cells from either aborted fetal tissue or embryos that remain following clinical *in vitro* fertilization (IVF) procedures involves the intentional destruction of a genetically unique, living member of the human species. According to this view, it is impermissible to obtain stem cells from *in vitro* fertilized blastocysts, because doing so results in the destruction of the blastocyst—a human life worthy of full moral protection from the moment of conception. No amount of benefit to others can justify the destruction of the blastocyst, an act that would be equivalent to murder.

Similarly, from this perspective, it is impermissible to obtain EG cells from the gonadal tissue of aborted fetuses, because although such harvesting is not directly responsible for the death of the fetus, it nevertheless involves complicity with the evil of abortion. Moreover, to make use of any therapy derived from research on either human embryonic or fetal tissue and to contribute to the development or application of such research through general taxation would involve complicity in the destruction of human life. Federal funding, which in a sense would make all citizens complicit in this research, thus would greatly impose upon the consciences of Catholics.

However, even the restrictive position of the Roman Catholic Church does not oppose stem cell research per se. The central moral impediment to such research concerns the sources from which stem cells are derived. The act of harvesting stem cells from other sources—miscarried fetuses, placental blood, or adult tissues—would not be intrinsically immoral. In fact, this perspective, recognizing the potential benefits to human health of stem cell research, encourages investigation into the feasibility of

such alternative sources. In practice, however, stem cell research, even with alternative stem cell sources, would remain morally problematic for two reasons. First, some are concerned that any safeguards will be ineffective because, in the face of potentially promising and lucrative research, the temptation to transgress such safeguards might be irresistible. Second, many fear that the benefits of this research might not be distributed equitably and are concerned that stem cell research perhaps may not be the best use of national resources, given the preponderance of so many other unmet human needs.

Although all Roman Catholics share a variety of important basic convictions, individual Catholics often differ in how to interpret them in practice. According to a less restrictive Catholic perspective, this disagreement is due, at least in part, to a commitment to the theory of natural law—a commitment that, while a fundamental part of the Catholic tradition, also involves reliance upon an "imperfect science." A commitment to natural law involves belief in a moral order that can be "seen" by all human beings in the reality of creation itself. But because the act of "looking" entails "a complex process of discernment and deliberation, and a structuring of insights, a determination of meaning, from the fullest vantage point available, given a particular history—one that includes the illumination of Scripture and the accumulated wisdom of the tradition"—what any two human beings see will not always be the same.[1]

With respect to stem cell research, the major areas of disagreement among Catholics are also those upon which the restrictive voice within Catholicism most strongly bases its opposition: the moral status of the embryo and the moral permissibility of using aborted fetuses as sources of stem cells. In contrast to this restrictive view of the embryo, another Catholic might, with the aid of science, look to the reality of the early human embryo and see that which is not yet an "individualized human entity with the settled inherent potential to become a human person."[2] Because the early embryo, according to this less restrictive view, is not a person, it is sometimes permissible to use it in research, though as human life it must always be accorded some respect. Similarly, one might decide that adequate barriers—such as a prohibition against the directed donation of cadaveric fetal tissue, and the distinction between somatic cell nuclear transfer (SCNT) for research or therapy and SCNT for reproduction—can be erected between the use of aborted fetal tissue in research and the act of abortion itself so that engaging in the former does not amount to complicity in the latter. From this perspective, then, a Catholic may be able to support ES cell research without sacrificing a commitment to the fundamental principles that define Catholicism, including the duties to protect human life, honor the sacred, and promote distributive justice in health care. Finally, because of the diversity within and among ethical traditions, this perspective is congruent with the restrictive Catholic view that individuals who oppose this research should not be forced to contribute to it but, contrary to the restrictive view, favors an approach that would allow federal funding, but with accommodations made to permit conscientious objection.

To summarize the testimony of the Roman Catholic panel, all agree that in light of certain agreed-upon principles, major Catholic concerns with regard to both embryonic and nonembryonic stem cell research include the following issues: 1) the moral status of the early embryo, 2) complicity with abortion in using fetal tissue as a source of stem cells, 3) the need for safeguards, distributive justice, and just allocation of national resources, and 4) the difficulty in federally funding research to which many are opposed on moral and religious grounds. The major disagreements arise from conflicting interpretations of the broad principles, which in turn lead to different responses to these four major concerns.

Jewish Perspectives

The two main sources of Jewish ethics—theology and law—yield several principles relevant to a Jewish ethical analysis of stem cell research. First, human beings are merely the stewards of their bodies, which belong to God. Moreover, God has placed conditions on the use of the human body, including the command that health and life must be preserved. Second, human beings are God's partners in healing, and in order to fulfill God's command, they have a duty to use any means available to heal themselves, whether these means are natural or artificial. Third, because all human beings, regardless of

ability, are created in the image of God, they are valuable. Fourth, human beings, unlike God, lack perfect knowledge of the consequences of their actions and in the process of trying to improve themselves or the world must, therefore, be careful to avoid causing harm to them.

Four potential moral impediments to EG and ES cell research arise from these Jewish principles: 1) the moral status of the fetus and of the act of abortion, 2) potential complicity with evil, 3) the commandments to respect the dead, and 4) the moral status of the embryo.

According to Conservative Judaism, the fetus until the 40th day after conception is "like water." Although the fetus becomes a potential and partial person after the 40th day, and is thus entitled to a certain amount of respect and protection, it remains primarily a part of the pregnant woman's body, and does not become an independent person with full moral rights until the greater part of its body emerges from the womb during birth. Because of the command to preserve human health and life, if either the health or the life of the woman is clearly threatened by the fetus, abortion is not only permissible but obligatory, as she is a full person while the fetus remains only a part of her and a potential person. When the woman's health is at some increased risk but is not clearly compromised by the pregnancy, abortion is permissible but not obligatory. More recently, some Jewish authorities also permit abortion in cases in which the fetus has a terminal disease or serious malformations.

According to Orthodox Judaism, on the other hand, after 40 days of gestation, the fetus becomes a person with full moral rights and may not be aborted except to protect the pregnant woman's health. Yet, even though abortion after 40 days is viewed by the Orthodox Jews as homicide, it does not follow from this perspective that life-saving use of stem cells procured from illegitimately aborted fetuses is impermissible (although the question of who can legitimately give consent to such procurement is problematic from this perspective). Although this perspective recognizes the possibility that therapeutic use of aborted fetuses may make abortion appear less heinous, the strength of the commandment to preserve life, for which all other laws must be suspended except those prohibiting murder, idolatry, and sexual transgressions, overrides this concern. Thus, despite the disagreement within Judaism regarding the moral status of the fetus and the permissibility of abortion after 40 days, all agree that neither source of stem cells is illegitimate. One caveat to this consensus is that some within Conservative Judaism who accept the permissibility of abortion to preserve the life or health of the woman nevertheless require that stem cells be procured only from fetuses that have been legitimately aborted; Orthodox Judaism, by contrast, appears to hold that although abortion after 40 days postconception is generally impermissible, there is no complicity involved in using these aborted fetuses as sources of stem cells.

Jewish thinkers agree that commandments to respect the dead, which require that corpses not be mutilated or left unburied longer than necessary, can be suspended in order to save lives. Because of the strong commandment to preserve life and health, for example, Jewish law permits both autopsies and organ procurement when they will benefit the living. Reasoning by analogy, if tissue procurement from the cadavers of full persons in order to benefit human health and life is permitted, then tissue procurement from dead fetuses—which according to some Jewish perspectives are less than full persons—must also be permitted for the same purpose provided that (for some interpreters) the abortion itself was permissible according to Jewish law.

There is also wide consensus within Judaism that no serious moral impediments exist to using IVF embryos as sources of stem cells because extra-corporeal embryos have no status under Jewish law. These entities lack status because all embryos prior to 40 days postconception are "like water" and because as extra-corporeal entities, they lack the status of potential and partial person that is accorded to fetuses, which develop from embryos implanted in a uterus. Although extra-corporeal embryos merit a certain respect as human life, they are closest in moral status to gametes and thus may be discarded, frozen, or used as life-saving sources of stem cells. In fact, so long as they are never implanted, there is no clear legal prohibition against creating embryos for research purposes, although extra-legal norms may raise ethical questions about this practice.

Because stem cells can be permissibly procured either from extra-corporeal embryos or from legitimately aborted fetuses, stem cell research is not considered intrinsically immoral. Rather, stem cell research becomes morally problematic when applied in a variety of contexts. First, Judaism views the provision of health care as a communal duty. Thus, a context in which the benefits of stem cell research are not accessible to all persons who are in need would be problematic. Similarly, it may be problematic to focus national resources in this area of research rather than in other areas of need. In addition, although obtaining consent to procure stem cells is necessary, it may be challenging. Finally, there is widespread agreement that stem cell research should not be used to enhance human beings, although some disagreement exists over whether it may be used to improve health or whether it must be reserved only for life-saving purposes.

Eastern Orthodox Perspectives

According to Eastern Orthodoxy, all human beings are created in the image of God and grow continuously toward the likeness of God. Although the embryo, fetus, and adult are each at different stages of this process, all share the same potential for attaining authentic personhood, and each, with God's grace, will attain such personhood. According to this belief, God has given us medicine in order to heal, and any misuse of this gift that results in the destruction of potentially authentic persons is considered illegitimate. Thus, although miscarried fetuses may be used as sources of EG cells, neither electively aborted fetuses nor blastocysts may be so used. However, despite the impermissibility of procuring ES cells from blastocysts, because cell lines from this source already exist and have the potential to save lives, it is considered wasteful to discard these lines, and it is in fact permissible to use them. No complicity is thought to arise from such use. On the other hand, it is not permissible to procure EG cells from aborted fetuses, as such procurement *would* involve complicity.

Even assuming that stem cells could be permissibly procured, Eastern Orthodoxy shares with other religious traditions a variety of concerns about the context in which stem cell research might be applied, including addressing the problems of equitable access to the benefits of the research and other problems that can occur when market forces control the research; using the research for eugenic or cosmetic purposes, rather than for healing; and obtaining the informed, voluntary consent of the woman or couple.

Islamic Perspectives

Islam consists of two major schools of thought—Sunni and Shi'i—both of which refer to the same historical sources. Although these two schools differ somewhat in their views of abortion, in general, Islam regards the life of the fetus as developing over several stages, and personhood is considered a process. Although from the moment of conception the embryo is a human life meriting some protection, it is not commonly thought to attain personhood until it is ensouled, some time around the fourth month of gestation. Thus, because of the enormous potential to improve human health through this type of research, the vast majority of followers of Islam would agree that it is permissible to use early human embryonic life for this purpose. Moreover, it is permissible to use the tissue from illegitimately aborted fetuses to save lives, just as it is permissible to use cadaveric organs to save lives, even when the cadaveric organ source has been wrongfully killed. Finally, with caution, it can be deduced that creating embryos for research purposes is also permissible from an Islamic perspective, as long as those embryos are not implanted.

Protestant Perspectives

Protestant positions range dramatically from the highly restrictive to the nonrestrictive in this area. For example, according to restrictive Protestant view, a person is not defined by his or her capacities; rather, a person is a human being with a personal history, regardless of whether he or she is aware of that history. From this perspective, embryos are simply the weakest and least advantaged people among us. Because procuring stem cells from embryos requires the destruction of the embryo, such procurement thus raises serious moral issues, despite the ease with which it might be used to

attain undeniably positive consequences for others, and rather than accepting the use of illicit means to achieve a good end, we should search for alternative, permissible means. Similarly, using aborted fetuses as sources of EG cells amounts to complicity with evil, and procurement of EG cells even from permissibly aborted fetuses (however that category is defined) would involve using a human life twice for another's benefit—first, to benefit the woman who aborted and then to benefit society through EG cell research. Therefore, from this perspective, it is impermissible to derive stem cells from embryos, whether spare or created for this purpose, and from aborted fetuses, whether permissibly aborted or not. The use of alternative sources of stem cells—for example, from bone marrow or umbilical cord blood—would, however, be permissible.

For Protestants whose views are less restrictive on this issue, the moral status of the embryo is more ambiguous. Although even nascent human life—which retains the potential for full human life—deserves respect and protection from callous disregard, the early embryo and the late fetus are viewed in moral terms as significantly different. Because the potential benefits of ES and EG cell research are so substantial, the moral difference between the early embryo and the developed fetus becomes compelling in this case, and it is thus permissible to use human life at the blastocyst stage to benefit other lives. No embryos should be created solely for this purpose, however, unless no other sources are available, and attempts should be made to locate alternative sources of stem cells that do not involve the destruction of embryos. It is permissible to procure EG cells from aborted fetuses, as long as safeguards are erected to prevent the therapeutic use of aborted fetal tissue from either increasing the frequency of abortion or encouraging a callous view of early human life. Moreover, although less restrictive Protestant views permit the procurement of stem cells from both proposed sources, this procurement must occur within a context of respect for nascent human life, only when significant benefit can be derived from it, and only after broad public discussion and acceptance of such research. If the general public is excluded from a discussion of this research, then public support of this and future beneficial research may be compromised. Furthermore, the requirement that all members of society have the opportunity to participate in open, sustained dialogue about these decisions is critical from this perspective, and if federal funds are to be allocated toward this research, conscientious objectors should be accommodated. Finally, most Protestants share previously articulated contextual concerns regarding 1) ensuring global access to the benefits of this research, 2) avoiding the negative consequences that might come with market-controlled research, and 3) assessing the priority of these research efforts relative to other current and pending health-related research projects.

Summary of Broad Areas of Agreement and Disagreement

Not surprisingly, the panelists did not reach unanimity on all aspects of human ES and EG cell research. Although some differences exist among the various religious traditions, these mostly concern the appropriate sources and methods of religious-ethical reasoning. On substantive issues, less restrictive individuals across most religious traditions appear to have more in common with each other than with restrictive members of their own faiths. (The same is true for commonalities among restrictive members of all faiths.) The substantive issues relevant to stem cell research on which there is internal disagreement include the following:

1) *The moral status of the embryo.* The perceived status of the embryo ranges from full moral personhood with correlative inviolable rights to life to an early, extracorporeal biological entity lacking any significant moral status. Between these poles, although the embryo tends to be viewed as valuable because of its current status as a form of human life and its potential status as a person, it is ultimately, if tragically, subordinate to the health needs of actual persons.
2) *Whether the use of EG cells derived from aborted fetuses involves complicity with the perceived evil of abortion.* On one end of the spectrum is the view that many abortions are permissible. Thus, complicity with evil is either never or rarely a consideration. On the other end of the spectrum is the view that all deliberate abortions are immoral, and that any use of EG cells derived from aborted fetuses involves complicity.

Those who take more moderate positions argue that even when abortion is wrong, it is not wrong to use tissue that would otherwise be discarded, or that complicity can be avoided by erecting barriers between abortion and stem cell procurement, such as a prohibition of directed donation.

3) *Whether stem cell research should, ideally, be federally funded.* Some, based on their belief in the duty to heal, hold that stem cell research should proceed as quickly as possible (given certain conditions; see below), while others hold that any federal funding that enables immoral research is itself immoral and would involve conscientious citizens in complicity against their will. The moderate view holds that in the absence of agreement on such issues as the moral status of the embryo, conscientious objectors should be allowed to opt out of federal support for the research and that without any federal support, privatized human ES and EG cell research will make contextual goals such as distributive justice even more difficult to realize.

Despite these areas of disagreement, widespread consensus was reached both within and among the various religious traditions on several important issues in ES and EG cell research:

1) Stem cell research is not inherently immoral, and in fact has the potential to contribute important knowledge that can lead to therapies for certain diseases, provided that morally legitimate sources of cells are used (although this is defined differently), and provided that important contextual factors of justice and regulation are addressed. (See #3 below.)
2) If society chooses to embark upon federally funded ES and EG cell research, it must do so under conditions of respect for the humanity of the embryo. It would be preferable if there existed alternative sources of stem cells that did not involve the direct or indirect destruction of human life, and efforts should be made to identify such sources.
3) In order for the research to be morally permissible, several "background factors" must be in place, including
   - assurance of equitable access to the benefits of the research,
   - appropriate prioritization of this research relative to other social needs,
   - assurance that the research will be used to treat disease, not enhance humans,
   - public education, discussion, and acceptance of human stem cell research, and
   - public scrutiny, oversight, and regulation of the research.
4) Assuming that privately funded research will continue in this area, it is preferable that a public body—even one that is funded with tax dollars—be required by law to review all private sector research and to make this review part of the public record, despite the possibility that the connection between the government and ES and EG cell research may be perceived as legitimating research that some citizens will continue to consider immoral.

Meeting Participants

Catholicism
Kevin W. Wildes, S.J., Ph.D., Georgetown University
Edmund D. Pellegrino, M.D., Georgetown University
Margaret Farley, Ph.D., Yale University

Judaism
Rabbi Elliot N. Dorff, Ph.D., University of Judaism
Rabbi Moshe Tendler, Ph.D., Yeshiva University
Laurie Zoloth, Ph.D., San Francisco State University

Eastern Orthodoxy
Father Demetrios Demopulos, Ph.D., Holy Trinity Greek Orthodox Church

Islam
Abdulaziz Sachedina, Ph.D., University of Virginia

Protestantism
Gilbert C. Meilander, Jr., Ph.D., Valparaiso University
Nancy J. Duff, Ph.D., Princeton University Theological Seminary
Ronald Cole-Turner, M.Div., Ph.D., Pittsburgh Theological Seminary

Notes

1 Farley, M., "Roman Catholic Views on Research Involving Human Embryonic Stem Cells." Testimony before NBAC. May 7, 1999. Washington DC. Meeting transcript, 3.

2 Ibid. 5.

Appendix F

Points to Consider in Evaluating Basic Research Involving Human Embryonic Stem Cells and Embryonic Germ Cells

This document describes some of the ethical, scientific, and legal issues that could be considered when designing and/or reviewing studies that involve access to and use of human stem cells. These *Points to Consider* are relevant only for designing and evaluating studies in which the role of the individual(s) who provide gametes, cadaveric fetal tissue, or embryos is limited to providing these materials for research intended to develop generalizable new knowledge. This document results from the recommendations described in this report and therefore is intended for use by those who design, conduct, and review research involving human embryonic stem (ES) and embryonic germ (EG) cells using federal funds. Private researchers and sponsors also may find this document to be of use. These *Points to Consider* do not apply to situations in which an individual would be the recipient of a stem cell-based therapy, nor do they apply to studies involving human/animal hybrids.

I. Scientific and Research Design Considerations

The ethical acceptability of any research protocol depends, in part, on its scientific merit, the qualifications of investigators, the protocol's overall design characteristics, and the precise nature of the materials and operations employed. In these respects, several issues arise when designing research involving human ES and EG cells, consideration of which would help ensure not only that the research is well designed, important, feasible, and timely, but also that a number of important ethical matters are considered. These issues are of particular significance given the nature of the materials to be used in research.

A. What are the sources from which human ES and EG cells will be obtained?
   1. From existing cell lines
   2. From cadaveric fetal tissue (following elective abortion or surgical termination of ectopic pregnancy)
   3. From embryos remaining after infertility treatments
   4. From embryos created solely for research purposes[1]

B. Has previous and requisite research been conducted using nonhuman animal models?

C. Are there valid alternatives to using human ES and EG cells in the proposed research?

D. What are the future plans for conservation of gametes, cadaveric fetal tissue, and embryos?
   1. Will ES or EG cells be produced and stored for later use?
   2. If a particular protocol is being proposed that uses embryos remaining after infertility treatments, does it propose to use only the minimum number of embryos necessary?
   3. What plans exist in the event that additional ES or EG stem cells are needed?

E. In what setting will the research be conducted?
   1. Are the investigators scientifically qualified to carry out the proposed research?
   2. Is the research environment (including facilities) appropriate for the conduct of research involving stem cells?

II. Identification of Providers and Donors and Recruitment Practices and Compensation

Several issues should be considered when identifying individuals (or couples) who may be asked to consider providing gametes, fetal tissue, or embryos for research; consideration of these issues could help to ensure that no inappropriate burden, inducement, or exploitation would occur.

A. Identification and recruitment practices
   1. Are potential donors or providers identified through advertisements to the general public? Are they identified through direct solicitation? Do they self-select?
   2. Is the selection of such individuals equitable and fair?
   3. Are these individuals vulnerable to undue influence, coercion, or exploitation? Does the recruitment method raise concerns about undue influence or coercion of the prospective donors?
   4. Are the potential donors capable of consenting?
   5. In which circumstances is it appropriate to identify and recruit an individual as well as his or her partner?

B. Compensation and reimbursement
   1. Will any financial compensation be paid to individuals (or couples) who donate materials; and if so, will the details of this compensation be disclosed?
   2. Does the compensation reimburse the individual (or couple) solely for the additional expenses that relate to this particular project?
   3. When is the offer of compensation made relative to an individual's (or couple's) decision to make available the materials from which stem cells will be derived?

III. Consent to Donate

Several issues arise in the process of providing information to individuals and couples who may be donating cadaveric fetal tissue or embryos remaining after infertility treatments. Considering these issues would help to ensure that prospective donors or providers of source materials would receive timely, relevant, and appropriate information to make informed and voluntary choices. In some cases, these issues are unique to the provision of gametes, embryos, or fetal tissue; in other cases. the items are important in other situations as well.

A. General considerations for individuals (or couples) who donate cadaveric fetal tissue or embryos remaining after infertility treatments
   1. Who will seek the consent? Will a clinician and/or researcher be available to answer questions?
   2. Is it appropriate for others to participate in the consent process (e.g., partner or family member)?
   3. Will psychological support mechanisms be in place if needed?
   4. Are the purposes of ES or EG cell research (in general) described fully?
   5. Will the consent form clearly disclose that stem cell research is not intended to benefit the donor directly?
   6. Is it clear that decisions to consent to or refuse the procedures to obtain stem cells will not affect the quality of care the patient will receive?
   7. Will individuals be informed that no medical or genetic information about the fetal tissue, embryos, or stem cells derived from these sources will be available to any outside individual or entity?
   8. What measures will be taken to protect the privacy and confidentiality of individuals who provide cadaveric fetal tissue or embryos?
   9. Is the source of funding for the research (public, private, public/private, philanthropic) disclosed?
   10. What known commercial benefits, if any, are expected to arise for the investigators seeking to obtain human ES or EG cells?

B. Additional considerations specific to consent to donate cadaveric fetal tissue
   1. Is there a description of what usually is done with fetal tissue at the institution at which a pregnancy will be terminated? Is this information available in written form and provided to individuals?
   2. Is permission to conduct research immediately available?

C. Additional considerations specific to consent to donate embryos remaining after infertility treatments
   1. Are the methods of disposal of embryos remaining after infertility treatments described? Is this information available in written form and provided to patients?
   2. Will information be made available about whether the embryos were viable and normal or not?
   3. Is there a description of the options available (e.g., permit material to be used in research, cryopreserve, discard, or donate to another couple for infertility treatment)?
   4. Is it clear that the embryos used in research will not, under any circumstances, be transferred to any woman's uterus?
   5. Is it clear that the research will result in the destruction of the embryo? Is the method described?

IV. Review Issues

Because of the special nature of human ES and EG cells, several issues arise in the review and oversight of research involving their use. The Commission has recommended a system of national oversight and review, combined with local monitoring. Careful and thoughtful consideration of these issues will provide assurance that, regardless of the source of funding, appropriate compliance with applicable regulations, guidelines, and other standards will occur. These considerations would supplement, not replace, applicable federal and state regulations.

A. Applicability of relevant regulations
   1. What current guidelines, regulations, rules, or policies apply to the conduct of this research? If ambiguity exists, how will it be resolved?
   2. What mechanisms are in place to assure compliance with these regulations?
   3. What regulations apply for collaborating with international researchers (e.g., importing fetal tissue or embryos from other countries)?

B. Applicability of professional practice standards

C. Submission of research findings for publication

D. Other responsibilities of investigators and collaborating clinicians

Note

1 The National Bioethics Advisory Commission has recommended that federal agencies should not fund research involving the derivation or use of human ES cells from embryos created solely for research purposes. (See Recommendations 3 and 4.)

Appendix G

Public and Expert Testimony

January 19, 1999 (Washington, DC)

Public:
E.J. Suh, Collegians Activated to Liberate Life
Kneale Ewing, Collegians Activated to Liberate Life
Olga Fairfax
Will Goodman

Expert:
Harold Varmus, National Institutes of Health
John Gearhart, The Johns Hopkins University
James Thomson, University of Wisconsin
Austin Smith, University of Edinburgh
Daniel Perry, Alliance for Aging Research
Patricia King, Georgetown University School of Law
John Robertson, University of Texas School of Law
Erik Parens, The Hastings Center
Françoise Baylis, Dalhousie University
Ted Peters, Center for Theology and the Natural Sciences
Karen Lebacqz, Pacific School of Religion

February 2–3, 1999 (Princeton, New Jersey)

Expert:
David Blumenthal, Massachusetts General Hospital
Brigid Hogan, Vanderbilt University
Barbara Mishkin, Hogan & Hartson L.L.P.
Robert Brady, Hogan & Hartson L.L.P.

March 2–3, 1999 (Vienna, Virginia)

Expert:
John Fletcher, University of Virginia
Lori Knowles, The Hastings Center
LeRoy Walters, Georgetown University

April 16, 1999 (Charlottesville, Virginia)

Public:
Richard Doerflinger, National Conference of Catholic Bishops
Edward Furton, National Catholic Bioethics Center
Karen Poehailos
Sidney Gunst, Jr.
Ida Chow, American Society of Cell Biology
Ethics and Religious Liberty Commission of the Southern Baptist Convention (submitted written testimony)

May 7, 1999 (Washington, DC)

Public:
Dena Davis, Cleveland-Marshall College of Law
Richard Doerflinger, National Conference of Catholic Bishops

Expert:
Kevin Wildes, Georgetown University
Edmund Pellegrino, Georgetown University
Margaret Farley, Yale University
Demetrios Demopulos, Holy Trinity Greek Orthodox Church
Elliot Dorff, University of Judaism
Moshe Tendler, Yeshiva University
Laurie Zoloth, San Francisco State University
Abdulaziz Sachedina, University of Virginia
Gilbert Meilander, Jr., Valparaiso University
Nancy Duff, Princeton University Theological Seminary

May 11–12, 1999 (Northbrook, Illinois)

Public:
Daniel McConchie, Center of Bioethics and Human Dignity

Expert:
Lori Andrews, Chicago–Kent College of Law
Sander Shapiro, University of Wisconsin–Madison

June 28, 1999 (Washington, DC)

Public:
Phil Noguchi, Food and Drug Administration

Appendix H

Commissioned Papers

The following papers, prepared for the National Bioethics Advisory Commission, are available in Volume II of this report:

State Regulation of Embryo Stem Cell Research
Lori B. Andrews
Chicago-Kent College of Law

The Food and Drug Administration's Statutory and Regulatory Authority to Regulate Human Pluripotent Stem Cells
Robert P. Brady, Molly S. Newberry, and Vicki W. Girard
Hogan & Hartson L.L.P.

Quick Response: Use of Human Fetal Tissue in Federally Funded Research
Elisa Eiseman
RAND Science and Technology Policy Institute

Analysis of Federal Laws Pertaining to Funding of Human Pluripotent Stem Cell Research
Ellen J. Flannery and Gail H. Javitt
Covington & Burling

Deliberating Incrementally on Human Pluripotential Stem Cell Research
John C. Fletcher
University of Virginia

Bioethical Regulation of Human Fetal Tissue and Embryonic Germ Cellular Material: Legal Survey and Analysis
J. Kyle Kinner, Presidential Management Intern
National Bioethics Advisory Commission

Regulating Embryonic Stem Cell Research: Biomedical Investigation of Human Embryos
J. Kyle Kinner, Presidential Management Intern
National Bioethics Advisory Commission

International Perspectives on Human Embryo and Fetal Tissue Research
Lori P. Knowles
The Hastings Center

What Has the President Asked of NBAC? On the Ethics and Politics of Embryonic Stem Cell Research
Erik Parens
The Hastings Center

Locating Convergence: Ethics, Public Policy, and Human Stem Cell Research
Andrew W. Siegel
The Johns Hopkins University