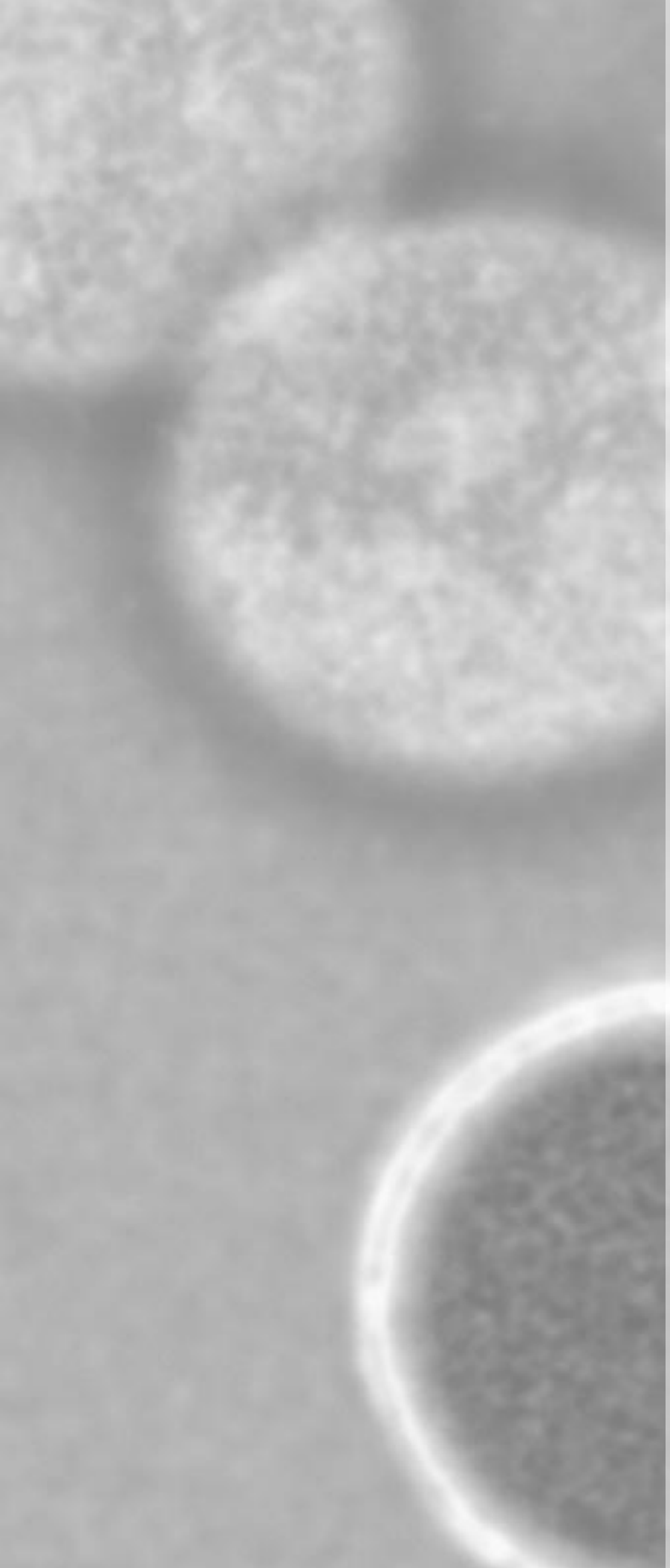

Ethical Issues in Human Stem Cell Research

Executive Summary

Rockville, Maryland
September 1999

The National Bioethics Advisory Commission (NBAC) was established by Executive Order 12975, signed by President Clinton on October 3, 1995. NBAC's functions are defined as follows:

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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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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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.