NATIONAL INSTITUTES OF HEALTH

Report of the

HUMAN EMBRYO RESEARCH PANEL

September 1994

Volume I

Report of the Human Embryo Research Panel

Ad Hoc Group of Consultants to the Advisory Committee to the Director, NIH

National Institutes of Health
Bethesda, Maryland

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Volume I

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Steven Muller
President Emeritus

October 12, 1994

Ruth L. Kirschstein, M.D.
Executive Secretary of the Advisory Committee
to the Director, NIH
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr. Kirschstein:

As Chairman of the panel established by the National Institutes of Health (NIH) to serve as *ad hoc* consultants to the Advisory Committee to the Director, NIH, to make recommendations to assist the development of guidelines for funding preimplantation human embryo research, and on behalf of the entire panel, I am pleased to forward the report of the NIH Human Embryo Research Panel for consideration by the Advisory Committee to the Director, NIH.

In response to Dr. Varmus' charge, the panel: (1) recommends NIH funding of certain areas of preimplantation embryo research within the framework of specified recommended guidelines; (2) identifies other areas of research of a particularly sensitive nature for which there should be a presumption against Federal funding for the foreseeable future, and then only on the basis of further consideration by a future formal review process; and (3) specifies several types of preimplantation embryo research which are deemed unacceptable for Federal funding on the basis of ethical considerations.

The panel first convened in February of this year and adjourned in September. During these eight months, the panel held six extensive meetings -- all open to the public; heard 46 oral presentations; and received over 30,000 letters, cards, and signatures on petitions as a panel, plus uncounted hundreds of items of correspondence addressed individually to panel members. From the first to the last day of the panel's work, there was constant and profound awareness of the high level of public concern about the sensitive and complex issues involved. The panel began

from the position that it was not called upon to decide which among the wide range of views held by American citizens on the moral status of preimplantation embryos is correct, but rather that its task was to make recommendations that would assist the NIH in developing guidelines for preimplantation human embryo research that took full account of generally-held public views regarding the beginning and development of human life.

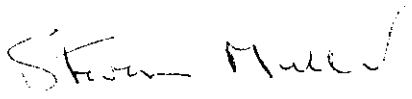
Much individual and collective soul-searching led to the panel's conclusions, and the report reflects the thinking and contribution of every member. The report as a whole has the unanimous concurrence of the panel's membership. It should, however, be noted that while the panel's decisions were reached by a majority in all cases, the majority was very narrow on several issues, as is noted in the report. In addition, five individual dissenting views on particular points were made. The panel's concurrence in the report as a whole also does not imply that every member completely agrees with all the wording or every recommendation. It is of course the panel's hope that the recommendations which it struggled so arduously to reach will assist the NIH in the development of sound public policy in an important and extremely sensitive area of biomedical research.

Absent Federal funding, other research on preimplantation human embryos in the private sector will doubtless continue to proceed without guidelines or adequate supervision. NIH funding would achieve much greater assurance that such research will be undertaken with adherence to carefully constructed guidelines and with carefully articulated safeguards and scrupulous review. In addition, Federal funding of preimplantation human embryo research would and should contribute significantly to public knowledge and understanding of this sensitive and vital area of biomedical science.

The panel owes a particular debt to Dr. Brigid L. M. Hogan, Co-Chair for Science, and Professor Patricia A. King, Co-Chair for Policy, for their distinguished leadership during the panel's deliberations.

It has been an honor and privilege to serve the National Institutes of Health and the Department of Health and Human Services, and I am confident that I speak for every member of the panel in thanking you for your confidence in providing us with this opportunity to serve.

Sincerely,



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Executive Summary

Charge to the Panel

The mandate of the National Institutes of Health (NIH) Human Embryo Research Panel (the Panel) was to consider various areas of research involving the ex utero preimplantation human embryo and to provide advice as to those areas that (1) are acceptable for Federal funding, (2) warrant additional review, and (3) are unacceptable for Federal support. For those areas of research considered acceptable for Federal funding, the Panel was asked to recommend specific guidelines for the review and conduct of this research.

The Panel's charge encompasses only research that involves extracorporeal human embryos produced by in vitro fertilization or from other sources, or parthenogenetically activated oocytes. Research involving in utero human embryos, or fetuses, is not part of the charge, since guidelines for such research are embodied in Federal laws and regulations governing human subjects research. Research involving human germ-line gene modification also is not within the Panel's scope. Therapeutic human fetal tissue transplantation research is also not part of the Panel's mandate; guidelines are already in place to govern such research.

Throughout this report, "ex utero preimplantation embryo" or "preimplantation embryo" refers to a fertilized ovum in vitro that has never been transferred to or implanted in a uterus. This includes a fertilized ovum that has been flushed from a woman before implantation in the uterus. This procedure, although infrequent and posing special risks, is included because it is one potential source of embryos.

Ethical Considerations

Throughout its deliberations, the Panel considered the wide range of views held by American citizens on the moral status of preimplantation embryos. In recommending public policy, the Panel was not called upon to decide which of these views is correct. Rather, its task was to propose guidelines for preimplantation human embryo research that would be acceptable public policy based on reasoning that takes account of generally held public views regarding the beginning and development of human life. The Panel weighed arguments for and against Federal funding of this research in light of the best available information and scientific knowledge and conducted its deliberations in terms that were independent of a particular religious or philosophical perspective.

The Panel received a considerable volume of public input, which it carefully considered. The Panel heard from citizens who object to any research involving preimplantation embryos as well as those who support it and listened closely to the thinking underlying the various opinions expressed. In the process of receiving public input, the Panel realized that the scientific and policy issues involved in research on preimplantation embryos are complex and not easily comprehended. The Panel therefore recognizes that a special effort is required to enhance public understanding of the issues related to research involving the preimplantation embryo. It is the Panel's hope that this report

will in some measure contribute to a process of increasing public awareness, discussion, and understanding of these issues.

From the perspective of public policy, the Panel concludes that sufficient arguments exist to support the permissibility of certain areas of research involving the preimplantation human embryo within a framework of stringent guidelines. This conclusion is based on an assessment of the moral status of the preimplantation embryo from various viewpoints and not solely on its location ex utero. In addition, the Panel weighed the important human benefits that might be achieved if preimplantation embryo research were federally funded under stringent guidelines.

The Panel believes that certain areas of research are permissible based on three primary considerations, which are listed below. Different members of the Panel may have accorded different weight to each of these considerations in reaching a conclusion about the permissibility of certain areas of research.

- The promise of human benefit from research is significant, carrying great potential benefit to infertile couples, families with genetic conditions, and individuals and families in need of effective therapies for a variety of diseases.

- Although the preimplantation human embryo warrants serious moral consideration as a developing form of human life, it does not have the same moral status as an infant or child. This is because of the absence of developmental individuation in the preimplantation embryo, the lack of even the possibility of sentience and most other qualities considered relevant to the moral status of persons, and the very high rate of natural mortality at this stage.

- In the continued absence of Federal funding and regulation in this area, preimplantation human embryo research that has been and is being conducted without Federal funding and regulation would continue, without consistent ethical and scientific review. It is in the public interest that the availability of Federal funding and regulation should provide consistent ethical and scientific review for this area of research. The Panel believes that because the preimplantation embryo possesses qualities requiring moral respect, research involving the ex utero preimplantation human embryo must be carefully regulated and consistently monitored.

Principles and Guidelines for Preimplantation Embryo Research

The Panel supports Federal funding of certain areas of preimplantation embryo research within the framework of the guidelines specified below. Any research conducted on the ex utero preimplantation human embryo or on gametes intended for fertilization should adhere to the following general principles as well as the more specific guidelines relevant to the nature of the particular research.

- The research must be conducted by scientifically qualified individuals in an appropriate research setting.

- The research must consist of a valid research design and promise significant scientific or clinical benefit.

- The research goals cannot be otherwise accomplished by using animals or unfertilized gametes. In addition, where applicable, adequate prior animal studies must have been conducted.

- The number of embryos required for the research must be kept to the minimum consistent with scientific criteria for validity.

- Donors of gametes or embryos must have given informed consent with regard to the nature and purpose of the specific research being undertaken.

- There must be no purchase or sale of gametes or embryos used in research. Reasonable compensation in clinical studies should be permissible to defray a subject's expenses, over and above the costs of drugs and procedures required for standard treatment, provided that no compensation or financial inducements of any sort are offered in exchange for the donation of gametes or embryos, and so long as the level of compensation is in accordance with Federal regulations governing human subjects research and that it is consistent with general compensation practice for other federally funded experimental protocols.

- Research protocols and consent forms must be reviewed and approved by an appropriate institutional review board (IRB) and, for the immediate future, an ad hoc review process that extends beyond the existing review process to be established by NIH and operated for at least 3 years.

- There must be equitable selection of donors of gametes and embryos, and efforts must be made to ensure that benefits and risks are fairly distributed among subgroups of the population.

- Out of respect for the special character of the preimplantation human embryo, research involving preimplantation embryos should be limited to the shortest time period consistent with the goals of each research proposal and, for the present, research involving human embryos should not be permitted beyond the time of the usual appearance of the primitive streak in vivo (14 days). An exception to this is made for research protocols with the goal of reliably identifying in the laboratory the appearance of the primitive streak.

Fertilization of Oocytes Expressly for Research Purposes

One of the most difficult issues the Panel had to consider was whether it is ethically permissible to fertilize donated oocytes expressly for research purposes or whether researchers should be restricted to the use of embryos remaining from infertility treatments that are donated by women or couples. In developing its recommendation concerning this issue, the Panel considered both the deeply held moral concerns about the fertilization of oocytes for research as well as the potential clinical benefits to be gained from such research. The Panel concludes that studies that require the fertilization of oocytes are needed to answer crucial questions in reproductive medicine and that it

would therefore not be wise to prohibit altogether the fertilization and study of oocytes for research purposes. The Panel had to balance important issues regarding the health and safety of women, children, and men against the moral respect due the preimplantation embryo. Given the conclusions the Panel reached about the moral status of the preimplantation embryo, it concludes that the health needs of women, children, and men must be given priority.

The Panel recognizes, however, that 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. There is also a possibility that if researchers had broad permission to develop embryos for research, more embryos might be created than is truly justified. 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. Examples of studies that might meet this condition include (1) oocyte maturation or oocyte freezing followed by fertilization and examination for subsequent developmental viability and chromosomal normalcy and (2) investigations into the process of fertilization itself (including the efficacy of new contraceptives). If oocyte maturation techniques were improved, eggs could be obtained without reliance on stimulatory drugs, lessening some of the potential risks for both patients and egg donors.

The second condition under which the fertilization of oocytes would be allowed expressly for research 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. One member of the Panel dissented from the Panel conclusion that under this condition oocytes may be fertilized expressly for research purposes (see appendix A).

Panel members believe that special attention is warranted for such research because of their concern that attempts might be made to create embryos for reasons that relate solely to the scarcity of embryos remaining from infertility programs and because of their interest in preventing the creation of embryos for any but the most compelling reasons. An example of studies that might meet this second condition is research to ensure that specific drugs used in reproductive medicine, such as those for inducing ovulation, have no harmful effect on oocytes and their developmental potential and do not compromise the future reproductive health of women.

In another case, future discoveries might provide strong evidence that some forms of infertility, birth defects, or childhood cancer are due to chromosomal abnormalities, DNA modifications, or metabolic defects in embryos from gametes of men and women of a particular category—for example, those exposed to specific environmental agents or carrying specific genetic traits. In order to test or validate such hypotheses, a compelling case might be made for comparing embryos from at-risk couples with control embryos from "normal" couples. While embryos from many infertile couples in in vitro fertilization (IVF) programs might be suitable for this control group, in specific cases a compelling argument might be made that gametes donated by fertile individuals carefully matched for age and ethnic background to those in the at-risk group are necessary for the most accurate and informative comparative scientific data.

Sources of Gametes and Embryos for Research

Having concluded that Federal funding of certain areas of preimplantation embryo research is acceptable within stringent guidelines, the Panel went on to address another set of ethical dilemmas raised by the issue of acceptability of various sources of gametes and embryos. In considering these issues the Panel identified four concerns that require special vigilance: the need for informed consent, limits on commercialization, equitable selection of donors for research, and appropriate balancing of risks and benefits among subgroups of the population. These concerns parallel those addressed by well-established ethical guidelines for all human research. The selection of sources of gametes and embryos for research must be consistent with these established guidelines and in addition must show respect for the special qualities of the human gamete and embryo.

The Panel gave careful consideration to the two distinct means by which a preimplantation human embryo can become available for research. The first occurs when embryos already fertilized for infertility treatments are not used for that purpose but are donated by the progenitors for research (these embryos are sometimes referred to as "spare" embryos). The second occurs when an oocyte is fertilized expressly for the purpose of research. The Panel also considered the ethical acceptability of the various donor sources of oocytes for research involving transfer, research without transfer, and research involving parthenogenesis. These possible donor sources include women in IVF programs, healthy volunteers, women undergoing pelvic surgery, women and girls who have died, and aborted fetuses.

In analyzing the acceptability of donor sources of gametes and embryos for research, the Panel emphasized that the risks of the research, including the risks of gamete procurement, must be in proportion to the anticipated benefits. Risks that occur at various stages of research and in the context of diverse protocols restrict the acceptable sources of research gametes and embryos. For example, the need to consider the well-being of the future child when embryos are transferred to the uterus mandates particular attention to the acceptability of gamete and embryo sources, including a requirement that the gamete donors approve of the research as well as the transfer.

In general, the Panel concludes that, provided all conditions regarding consent and limits on commercialization are met, embryos donated by couples in IVF programs are acceptable sources for basic research that does not involve transfer, as well as for clinical studies that may involve transfer. Women undergoing IVF treatment may also donate oocytes not needed for their own treatment, provided other guidelines are met. In this regard, the Panel believes it is right for women and couples undergoing infertility treatment to assume a fair share of the burden of advancing research in this area given that they, as a class, stand to benefit most from the clinical applications that may result. However, the Panel also recognizes that infertility can cause great physical and psychological pain and that women and couples undergoing treatment may be more vulnerable as a result. For this reason one member of the Panel dissents from allowing women in IVF treatment the opportunity to donate oocytes for research that does not involve transfer (see appendix A). In order that women and couples in IVF programs are not made to feel compelled to donate, great care must be taken to ensure that there is no undue, or even subtle, pressure to donate. The voluntary nature of such donations is essential, and under no circumstances should individuals who do not wish to donate their gametes ever feel pressured to do so.

Donation of oocytes for research purposes without intent to transfer raises special concerns regarding risks to women. Some of the methods used to procure eggs, especially hyperstimulation, involve the use of powerful drugs and invasive procedures that could pose risks to the health of women. Women undergoing treatment for infertility consent to these risks in return for potential therapeutic benefit and are an acceptable source of oocytes for basic research that does not involve transfer, as well as for clinical studies that may involve transfer.

Women undergoing scheduled pelvic surgery are an additional permissible source of oocytes for research, provided that other guidelines are met and that no additional risks are imposed. Researchers must explain any changes from standard surgical procedures and, if hormonal stimulation is used, the risks of such drugs.

Women who are not scheduled to undergo a surgical procedure are *not* a permissible source of oocytes for embryos developed for research at this time, even if they wish to volunteer to donate their oocytes. The Panel, however, is willing to allow such volunteers to donate oocytes if the intent is to transfer the resulting embryo for the purpose of establishing a pregnancy. This is because the risks to the donor undergoing oocyte retrieval may be justified by the potential direct benefit to the infertile couple who hope to become parents as a result of the procedure. Absent the goal of establishing a pregnancy for an infertile couple, the lack of direct therapeutic benefit to the donor and the dangers of commercial exploitation do not justify exposing women to such risks.

Women who have died are a permissible source of oocytes for research without transfer, provided that the woman had not expressly objected to such use of her oocytes and that appropriate consent is obtained. If the woman had expressed no objection to such use of her oocytes, either she must have consented to donation before her death or, in the absence of explicit consent on her part, next of kin may give consent at the time of her death. One member of the Panel dissents from this recommendation based on the belief that consent must have been obtained from the woman before her death (see appendix A). Care must be taken to ensure that the consenting donors, or their next of kin who would be providing proxy consent, are clearly and specifically aware that the organ being donated is the ovary and that it might be used in research that could involve the fertilization of any oocytes derived from it. It should also be made clear to donors and next of kin that transfer of any embryo created from such material to the uterus is prohibited.

Because of strong concerns about the importance of parenthood and the orderly sequence of generations, as well as the need for detailed medical histories, the Panel concluded that research involving the transfer of embryos created from oocytes obtained from cadaveric sources, including aborted fetuses, should be unacceptable for Federal funding. The Panel also felt that it would be unwise public policy at this time to support, without additional review, research involving the fertilization of fetal oocytes, even if not intended for transfer to the uterus. Such research should not be supported until the ethical implications are more fully explored and addressed by a national advisory body.

Transfer of Embryos to a Uterus

In addition to these general guidelines, the Panel developed specific guidelines for research on preimplantation embryos intended for transfer and for those not intended for transfer, as well as guidelines for research involving parthenogenesis.

It is important to recognize that when transfer to a uterus is intended, research on the preimplantation embryo can result in harm to the child who could be born, a research subject whose treatment raises distinct ethical issues. In both law and ethics it is clear that fetuses who are brought to term are considered persons with full moral status and protectability. It would therefore be unacceptable to transfer an embryo if it is reasonable to believe that a child who might be born from these procedures will suffer harm as a result of the research. Even when research involves a diagnostic procedure, an embryo may not be transferred unless there is reasonable confidence that any child born as a result of these procedures has not been harmed by them. This distinction in treatment between embryos that will be transferred and those that will not is warranted by the need to avoid harm to the child who could be born.

Parthenogenesis

In keeping with its mandate, the Panel also considered the acceptability of Federal funding of research involving the parthenogenetic activation of eggs. Parthenogenesis is the activation of eggs to begin cleavage and development without fertilization. It has been shown in research involving parthenogenesis in mammals that when such parthenotes are transferred to the uterus, few reach the stage of implantation. The few that do reach implantation develop to various stages of early cell differentiation but then lose capacity for further development and die. Parthenotes fail to develop further because they lack expression of essential genes contributed by the sperm. All evidence therefore suggests that human parthenotes intrinsically are not developmentally viable human embryos. Thus, they do *not* represent a form of asexual reproduction.

Research on parthenotes, or activated eggs, might provide information on the specific role of the egg mechanisms in activating and sustaining early development, without generating a human embryo. Parthenotes may have research utility nearly identical to the normal embryo up to the blastocyst stage. In addition, a certain type of ovarian tumor originates from eggs that develop as parthenotes while still in the ovary. Research on parthenotes may shed light on problems arising during oocyte development that promote this type of tumor formation.

The Panel recommends that research proposals involving parthenogenesis be considered ethically acceptable on the conditions that they adhere to the general principles and that transfer of parthenogenetically activated oocytes not be permitted under any circumstances. The Panel wishes to allay fears expressed by members of the public who are concerned about the end point of research on parthenogenesis. To many, such research appears to represent a tampering with the natural order in unacceptable ways. Even though it is considered intrinsically impossible in humans, the Panel would preclude any attempts to develop a fetus or child without a paternal progenitor by prohibiting research involving the transfer of parthenotes.

Review and Oversight of Research

The Panel does not recommend that an Ethics Advisory Board (EAB) be reconstituted for the purpose of reviewing research protocols involving embryos and fertilized eggs. Although revisiting the EAB experience offers the potential for developing public consensus and a consistent application of the new guidelines, it nonetheless has significant disadvantages. These disadvantages include the creation of an additional standing government board, the likelihood of a 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 further possible 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.

The Panel wishes to retain the strengths of the old EAB—such as its assurance of consistent application of guidelines—without creating a new regulatory body. Therefore, the Panel recommends that all research proposals involving preimplantation human embryo research that are submitted to NIH for funding or that are proposed for conduct in the NIH intramural research program be subject to an additional review at the national level by an ad hoc body created with the discretionary authority of the Director of NIH. Two members of the Panel formally dissent from this recommendation, citing the adequacy of existing review through local IRBs and the possibility of such a review board being subject to undue pressures.

The purpose of the recommended review is to ensure that such research is conducted in accordance with guidelines established by NIH. This review is in addition to existing procedures and should occur after the standard reviews and approvals by the study section and council have been completed. The additional review process should continue for at least 3 years. If the NIH Director elects to dissolve this ad hoc review process after 3 years, a more decentralized review with certain additional oversight provisions, as specified further below, should begin.

When the ad hoc review body ceases to exist, the Panel recommends that all such research proposals continue to be specially monitored by the NIH councils and the NIH Office for Protection From Research Risks. This monitoring would include a commitment by the councils to pay particular attention to the protocols as they are presented for approval, in order to ensure that the local IRB and NIH study section have correctly applied the guidelines adopted by the NIH Director.

Categories of Research

Consistent with its mandate, the Panel considered specific areas of research in terms of acceptability for Federal funding. While it is clearly impossible to anticipate every type of research project that might be proposed, the Panel was charged to divide types of embryo research into three categories: (1) acceptable for Federal funding, (2) warranting additional review, and (3) unacceptable for Federal funding.

Acceptable for Federal Funding

A research proposal is presumed acceptable if it is in accordance with the guidelines described above and is not described below as warranting additional review or being unacceptable. A protocol not in the last two categories would be classified acceptable if it is scientifically valid and meritorious; relies on prior adequate animal studies and, where appropriate, studies on human embryos without transfer; uses a minimal number of embryos; documents that informed consent will be obtained from acceptable donor sources; involves no purchase or sale of gametes or embryos; does not continue beyond the time of the usual appearance of the primitive streak in vivo (14 days); and has passed the required review by a local IRB, appropriate NIH study section and council, and, for the immediate future, the additional ad hoc review body at the national level established at the discretion of the NIH Director.

Proposals in the acceptable category must also meet the specific guidelines set forth in this report concerning types of research (i.e., transfer, no transfer, parthenogenesis) (see chapter 5), and acceptable sources of gametes and embryos. Examples of such proposals include, but are not limited to the following:

- Studies aimed at improving the likelihood of a successful outcome for a pregnancy.
- Research on the process of fertilization.
- Studies on egg activation and the relative role of paternally derived and maternally derived genetic material in embryo development (parthenogenesis without transfer).
- Studies in oocyte maturation or freezing followed by fertilization to determine developmental and chromosomal normality.
- Research involving preimplantation genetic diagnosis with and without transfer.
- Research involving the development of embryonic stem cells, but only with embryos resulting from IVF for infertility treatment or clinical research that have been donated with the consent of the progenitors.
- Nuclear transplantation into an enucleated, fertilized or unfertilized (but activated) egg without transfer for research that aims to circumvent or correct an inherited cytoplasmic defect.

With regard to the last example, a narrow majority of the Panel believed such research should be acceptable for Federal funding. Nearly as many thought that the ethical implications of research involving the transplantation of a nucleus, whether transfer was contemplated or not, need further study before the research could be considered acceptable for Federal funding.

In addition to these examples, the Panel singled out two types of acceptable research for special consideration in the recommended ad hoc review process.

- Research involving the use of existing embryos where one of the progenitors was an anonymous gamete source who received monetary compensation. (This exception would

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The Panel gave careful consideration to the two distinct means by which a preimplantation human embryo can become available for research. The first occurs when embryos already fertilized for infertility treatments are not used for that purpose but are donated by the progenitors for research (these embryos are sometimes referred to as "spare" embryos). The second occurs when an oocyte is fertilized expressly for the purpose of research. The Panel also considered the ethical acceptability of the various donor sources of oocytes for research involving transfer, research without transfer, and research involving parthenogenesis. These possible donor sources include women in IVF programs, healthy volunteers, women undergoing pelvic surgery, women and girls who have died, and aborted fetuses.

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about where to place the research. For research involving the development of embryonic stem cells from deliberately fertilized oocytes, a narrow majority of members agreed such research warranted further review. A number of other members, however, felt that the research was acceptable for Federal funding, while some believed that such research should be considered unacceptable for Federal funding. The Panel's deliberation about the use of fetal oocytes for research without transfer involved painstaking reflection about the ethical implications and public sensibilities. The decision to recommend that this research be placed in the further review category, rather than the unacceptable category, was made by a bare majority.

Unacceptable for Federal Funding

Four ethical considerations entered into the deliberations of the Panel as it determined what types of research were unacceptable for Federal funding: the potential adverse consequences of the research for children, women, and men; the respect due the preimplantation embryo; concern for public sensitivities about highly controversial research proposals; and concern for the meaning of humanness, parenthood, and the succession of generations.

Throughout its report, the Panel considered these concerns as well as the scientific promise and the clinical and therapeutic value of proposed research, particularly as it might contribute to the well-being of women, children, and men. Regarding the types of research considered unacceptable, the Panel determined that the scientific and therapeutic value was low or questionable, or that animal studies did not warrant progressing to human research.

Research proposals in the unacceptable category should not be funded for the foreseeable future. Even if claims were made for their scientific or therapeutic value, serious ethical concerns counsel against supporting such research. Such research includes the following:

- Cloning of human preimplantation embryos by separating blastomeres or dividing blastocysts (induced twinning), followed by transfer in utero.
- Studies designed to transplant embryonic or adult nuclei into an enucleated egg, including nuclear cloning, in order to duplicate a genome or to increase the number of embryos with the same genotype with transfer.
- Research beyond the onset of closure of the neural tube.
- Research involving the fertilization of fetal oocytes with transfer.
- Preimplantation genetic diagnosis for sex selection, except for sex-linked genetic diseases.
- Development of human-nonhuman and human-human chimeras with or without transfer.
- Cross-species fertilization, except for clinical tests of the ability of sperm to penetrate eggs.
- Attempted transfer of parthenogenetically activated human eggs.

- Attempted transfer of human embryos into nonhuman animals for gestation.
- Transfer of human embryos for extrauterine or abdominal pregnancy.

Need for Public Education

Finally, the Panel believes that any successful efforts in preimplantation embryo research depend on improving public understanding of the nature of preimplantation embryo research and therefore recommends that NIH undertake efforts toward public education as it simultaneously educates the scientific community about guidelines for acceptable research.

Chapter 1. Introduction

Until June 1993, Federal regulations governing research on human subjects (45 CFR 46) required that research involving in vitro fertilization (IVF) be reviewed by an Ethics Advisory Board (EAB). This procedural requirement established by the Department of Health and Human Services (HHS) required that

> No application or proposal involving in vitro fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.[1]

The EAB existed briefly from 1978 to 1980 and actually considered the ethical issues associated with IVF and embryo transfer. It concluded in one report that IVF and Federal funding of IVF research aimed at establishing the safety and efficacy of the technology were acceptable from an ethical standpoint as long as certain stipulated safeguards were followed. No action was taken on that report by the Secretary, and no EAB was chartered after 1980. Federal funding of IVF protocols was therefore not possible. With the enactment of the National Institutes of Health (NIH) Revitalization Act of 1993 (Public Law 103-43, section 121(c), the regulatory provision requiring EAB review of IVF proposals was nullified, removing an 18-year barrier to such research. As a result of the act, IVF research proposals, as well as research involving ex utero preimplantation human embryos (hereafter referred to as preimplantation embryos)[2] that result from IVF or other sources, may now be considered for Federal funding without the review of an EAB.

The report language accompanying the House and Senate bills leading to Public Law 103-43 makes the congressional intent in this regard quite clear. That language reads in part as follows:

> In particular, Section 492A will permit the funding of peer reviewed and approved research proposals involving assisted reproductive technologies including in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT).[3]
>
> Subsection (c) nullifies the de facto moratorium currently in place on federal support for research on human in vitro fertilization, a promising area of research on the treatment of infertility. Since 1979, this research has been effectively banned by HHS under regulations which require the approval of such research by an Ethics Advisory

[1] 45 CFR 46.204(d).

[2] Throughout this report, "ex utero preimplantation embryo" or "preimplantation embryo" refers to a fertilized ovum in vitro that has never been transferred to or implanted in a uterus. This includes a fertilized ovum that has been flushed from a woman before implantation in the uterus. This procedure, which is infrequent and poses special risks, is included because it is one potential source of embryos.

[3] Senate Report 103-2, p. 24.

> Board. Because no such Board has been appointed by the Secretary during the last 13 years, no review of any application for in vitro fertilization research has been allowed to go forward at NIH. The effect of this de facto moratorium has been to hobble this area of research, relying only on the private sector without regulation or clear ethical or medical guidelines.[4]

Until recently, most research involving preimplantation embryos has been conducted to improve the chances of pregnancy through laboratory-assisted conception. Virtually all the methods used currently in clinical situations for the preparation of spermatozoa, in vitro insemination of oocytes, and culture and cryopreservation of preimplantation embryos have been established in animal systems and in some cases use procedures and media developed over 25 years ago.[5] Nearly all research into molecular, cellular, and physiological aspects of early animal embryology has been supported by the Federal Government based on the understanding that advances in these areas can ultimately be applied to the human, especially in efforts designed to treat infertility.

More recently, research on the preimplantation embryo has been proposed that is much broader than therapies related to infertility. These research areas include the following:

- The process of embryo implantation, the maintenance of early pregnancy, and the prevention of early spontaneous miscarriages.
- Basic knowledge about normal early human development and the origin of certain birth defects.
- The preimplantation diagnosis of genetic or chromosomal abnormalities leading to severe inherited diseases.
- The origin of chromosomal abnormalities associated with infertility and with childhood cancers.
- Understanding the process of oocyte maturation and how eggs may be affected by environmental agents, including cryopreservation of oocytes from women undergoing chemotherapy or irradiation.
- The development of new contraceptives.
- Cancer and the process of metastasis.
- The development of pluripotent[6] embryonic stem cell lines for generating differentiated cells for transplantation and tissue repair.

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[4] House Report 103-28, p. 80.

[5] J. Van Blerkom, "The History, Current Status and Future Direction of Research Involving Human Embryos," a paper prepared for the NIH Human Embryo Research Panel, January 10, 1994. (See volume II of this report.)

[6] "Pluripotentiality" refers to the ability of cells to develop in any one of several different ways or to contribute to more than one organ or tissue.

Federal regulations currently cover research on the fetus, defined as the "product of conception from the time of implantation (as evidenced by the presumptive signs of pregnancy)."[7] Embryos are protected research subjects in current Federal law once they have actually implanted in a womb. At present, however, no NIH or HHS guidelines exist for research on embryos that have never implanted. However, guidelines have been developed in other countries and by professional and scientific societies in the United States.

As set forth in section 301 of the Public Health Service Act, the mandate of NIH is to advance scientific knowledge for the benefit of human health. A more specific mission and mandate to conduct and support research with respect to human growth and development, including prenatal development, population research, and special health problems and requirements of mothers and children, is set forth in section 448 of the act. These missions encompass health problems such as infertility, pregnancy loss, genetic disease, and cancer—all areas that might benefit from research involving the ex utero human embryo.

NIH has received a number of applications for support of research to improve the success of IVF and for research on embryos obtained through IVF but not intended for transfer in utero (sometimes referred to as "spare" embryos). Applications have also been received for support of research on parthenogenesis, a process by which activation of an ovum is initiated without sperm. Before proceeding with the consideration of specific human embryo research proposals for funding, however, NIH saw the need to address the profound moral and ethical issues raised by the use of human embryos in research and to develop guidelines to govern the review and conduct of federally funded research. Until such guidelines are developed, research involving the preimplantation human embryo is not being funded.

In August 1993, the Acting Director of NIH sent a request to the Assistant Secretary for Health for approval to establish a broad-based panel as a subcommittee of the Advisory Committee to the Director to recommend guidelines for funding preimplantation embryo research. This approval was granted in September 1993. The 19 individuals composing the panel (hereafter referred to as the NIH Human Embryo Research Panel, or the Panel) were selected on the basis of broad expertise in the fields of basic and clinical research, ethics, law, social science, public health, and public policy issues. Attention was also given to the Panel's balance according to gender, race, and ethnicity, and to geographic distribution, but not to the Panel members' positions on the acceptability of embryo research. The report of the Panel is subject to the review and acceptance of the Advisory Committee to the Director, NIH.

The charge to the Panel was to consider various areas of research involving the preimplantation embryo and to provide advice as to those areas that (1) are acceptable for Federal funding, (2) warrant additional review, and (3) are unacceptable for Federal support. For those areas of research considered acceptable for Federal funding, the Panel was asked to recommend specific guidelines for the review and conduct of this research.

The Panel's charge encompasses only research that involves extracorporeal human preimplantation embryos resulting from IVF or other sources or parthenogenetically activated oocytes. Research involving in utero human embryos, or fetuses, is not part of the charge since guidelines for

[7] 45 CFR 46.203.

such research are embodied in Federal laws and regulations governing human subjects research. Research involving human germ-line gene modification also is not within the Panel's scope. Therapeutic human fetal tissue transplantation research is also not a part of the Panel's mandate; guidelines are already in place to govern such research.

Panel Process

While NIH set forth the charge to the Panel, Panel members were given wide latitude in identifying the specific issues and questions that needed attention and the approach they would take in analyzing and addressing them. To help inform the Panel's deliberations, the NIH commissioned four scholarly papers on various topics relevant to the Panel charge. (The titles of these papers are listed in appendix G; the papers are incorporated as volume II of this report.)

The Panel met five times over a 5-month period from February 1994 to June 1994. All meetings were open to the public and provided an opportunity for public testimony. Public notice of all meetings of the Panel was published in the *Federal Register,* and over 250 professional organizations and interest groups were sent announcements. Also advised of the initiation of the Panel's activities were Members of Congress with legislative involvement in NIH programs.[8] During the Panel meetings, oral testimony was heard from 46 individuals or organizations. In addition, NIH received correspondence from more than 30,000 individuals via letters, postcards, and petitions on issues raised by research involving the ex utero human embryo. A significant portion of the correspondence also expressed views about research involving in utero fetuses and therapeutic fetal tissue transplantation research—matters outside the Panel's scope. Some of the correspondence also expressed opposition to abortion—another matter outside the scope of the research considered by the Panel. Individual Panel members also received a sizable, but undetermined, amount of correspondence.

In considering NIH funding for studies on preimplantation embryos, the Panel obtained information about the nature of the investigations that might be conducted; the clinical need for such work and its scientific and ethical justification; and the benefits, as well as problems, that might flow from it. The potential benefits were examined for their application in the short term to the relief of human suffering because of infertility and severe congenital defects and inherited diseases. However, it was also recognized that studies on preimplantation embryos could make important contributions over the long term to a variety of important medical problems.

Organization of the Report

The report of the Panel is organized around three themes central to its charge. Chapter 2 addresses the scientific issues in human embryo research, chapter 3 discusses the diversity of views on the moral status of the preimplantation human embryo and ethical frameworks for consideration of human embryo research, and chapter 4 outlines issues concerning sources of gametes and embryos for research. Based on careful consideration and lengthy discussion of these issues, the Panel developed

[8] Members of the relevant House and Senate authorizing and appropriating bodies as well as members of the Congressional Biomedical Research Caucus and the Congressional Caucus for Women's Issues.

general principles (chapter 5) to be applied in determining the acceptability of various areas of preimplantation embryo research, as well as to guide investigators whose work is funded. The Panel also recommends a process for review and monitoring of research in this area (chapter 5). Finally, in accordance with its mandate, the Panel delineated (chapter 6) areas of research considered acceptable for Federal funding, warranting additional review, and unacceptable for Federal support.

Chapter 2. Scientific and Medical Issues in Preimplantation Embryo Research

Introduction

From expert testimony and the study of published papers, the Panel learned that research on preimplantation embryos is already being carried out in many privately funded laboratories in the United States. It is the opinion of experts in human embryology[1] that much of the work in the United States has been of a quality lower than that done in other countries, in part because it has been directed by clinicians without experience in either basic research or developmental biology. The introduction of National Institutes of Health (NIH) funding and associated guidelines for ethical and scientific conduct would, it was argued, raise the standard of scientific inquiry and facilitate the interaction of clinicians with basic scientists.

In the course of its discussions, the Panel considered evidence that studies with preimplantation embryos could be of benefit in the following ways:

- By improving clinical protocols used in in vitro fertilization (IVF) programs for the treatment of male and female infertility.
- By introducing new and improved techniques for preimplantation diagnosis of genetic and chromosomal abnormalities associated with severe inherited disorders.
- By providing new, high-quality information about the morphology, biochemical and biophysical properties, genetic expression, and similar biological characteristics of pregastrulation-stage human embryos.
- By developing methods for maturing oocytes in culture to the stage when they can be fertilized and develop normally. This would facilitate the cryopreservation of oocytes for women undergoing chemotherapy and avoid the risk of hormonal hyperstimulation of oocyte donors, as well as lead to greater understanding of how environmental agents might damage eggs in vivo.
- By enhancing knowledge of the process of fertilization.
- By facilitating the design of new contraceptives.
- By providing more information about egg activation and the relative contribution of maternal and paternal genes to early development (through parthenogenesis).

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[1] J. Van Blerkom, "The History, Current Status and Future Direction of Research Involving Human Embryos," a paper prepared for the NIH Human Embryo Research Panel, January 10, 1994. (See volume II of this report.)

- By improving knowledge about the process of embryo implantation into the uterus, the maintenance of early pregnancy and maternal-fetal interactions, and the prevention of early spontaneous miscarriages.
- By providing basic knowledge about normal early human development up to gastrulation and the origin of certain birth defects.
- By increasing knowledge of the mechanisms of neurulation.
- By facilitating the isolation of pluripotential embryonic stem cell lines for eventual differentiation and clinical use in transplantation and tissue repair.
- By increasing knowledge about cancer and metastasis, including the causes of certain reproductive cancers.
- By exploring the use of nuclear transplantation to circumvent disorders due to maternal inheritance of cytoplasmic defects.

Each of the areas listed above is described in detail in this chapter. The Panel also considered two types of technologies that have been widely used with nonhuman embryos—namely, production of genetically identical copies of embryos (cloning) by embryo splitting and by nuclear transplantation. These are discussed separately under the subheading "Cloning."

Finally, the Panel believed that it was important for the sake of completeness to obtain scientific information about several other topics, such as cross-species fertilization, formation of human-nonhuman and human-human chimeras, and transfer of a human embryo into a nonhuman species. These subjects, which the Panel deemed proscribed for Federal funding, are described briefly under the subheading "Scientific Possibilities Proscribed for Federal Funding" (see also chapters 3 and 6).

In public discussions of issues associated with studies on preimplantation embryos, there has been some confusion about terminology, in particular the use of descriptors such as "preembryo," "preimplantation embryo," "conceptus," and "fetus." For clarity, the Panel attempted to be as specific and scientific as possible in its deliberations and to use terms such as "zygote," "blastocyst," "gastrulation," and "neurulation" to denote the stages of development of the embryo arising from a fertilized oocyte. The Panel uses the term "preimplantation" to describe the status of the embryo before transfer or implantation occurs. Throughout this report "ex utero preimplantation embryo" or "preimplantation embryo" refers to an ovum fertilized in vitro (or that has been fertilized in vivo and flushed from a woman before implantation in the uterus) that has never been transferred back to a uterus or has not yet implanted itself in a uterus.

Summary of Development of the Human Embryo Up to Closure of the Neural Tube

For clarity, a brief summary is given here of the development of the normal human embryo up to neurulation. During the preimplantation period, the human embryo consists only of a small

cluster of cells and is about 130 μm in diameter, significantly smaller than the period at the end of this sentence. Moreover, these cells are unspecialized; they do not form part of a coherent, organized, individual embryo, since one or more of them can be removed without affecting the development of the later fetus and one embryo can give rise to identical twins. The first specialization event occurs just before the embryo attaches to the uterus, around 6 to 7 days after fertilization, when the number of cells has reached about 100. The 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 that remain undifferentiated.

In the week after implantation, these inner cells give rise to more of the placental tissue and eventually to a small disk of cells from which the fetus will develop. By 14 days, the embryonic disk is still only about 0.5 mm in diameter and consists of about 2,000 cells. It is only 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, including primitive neural cells. Gastrulation is the process by which the bilaminar (two-layered) embryonic disk is converted into a trilaminar (three-layered) embryonic disk. Its onset at day 14 in vivo is heralded by the appearance of the primitive streak, a region in which cells move from one layer to another in an organized way. During the first stage of gastrulation, there is no human form, even a rudimentary nervous system is absent, and the cells giving rise to the fetus are unspecialized and identical in potential developmental fate.[2]

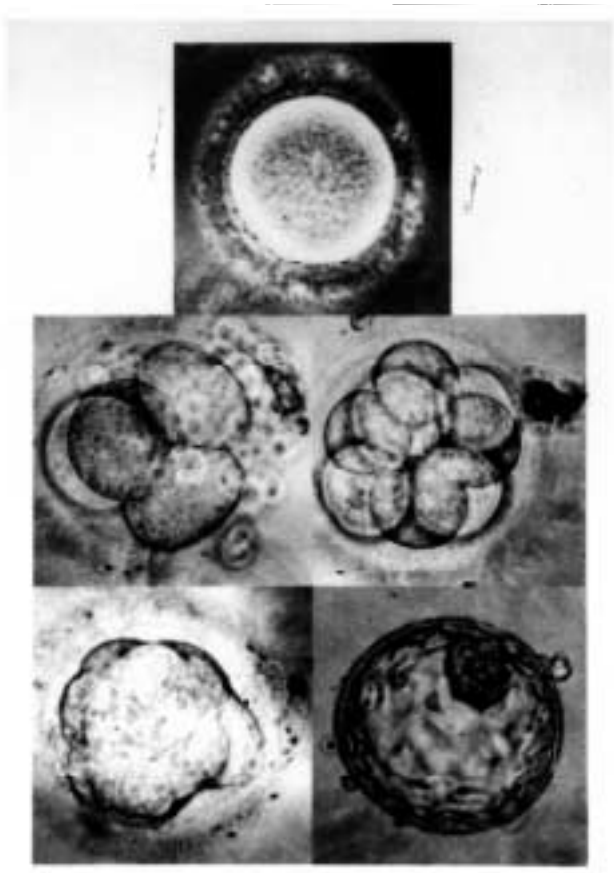

Figure 1. Summary of development.

Top: human oocyte; left center: four-cell embryo; right center: eight-cell embryo; bottom left: morula; bottom right: blastocyst, showing inner cell mass and trophectoderm. (*The Biochemist* 16(2):April/May 1994)

It has been noted that the "primitive streak . . . and notochordal process are clearly visible [at 15–16 days in vivo]: these are the morphologic indications characteristic of gastrulation."[3] Under the microscope, it is possible to visualize the primitive streak in a normal

[2] K.L. Moore and T.V.N. Persaud, *The Developing Human: Clinically Oriented Embryology*, 5th ed., (Philadelphia: W.B. Saunders, 1993); H. Tuchmann-Duplessis, G. David, and P. Haegel, *Illustrated Human Embryology, Vol. 1: Embryogenesis* (New York: Springer Verlag, 1982).

[3] H. Tuchmann-Duplessis, G. David, and P. Haegel, *Illustrated Human Embryology, Vol. 1: Embryogenesis* (New York: Springer Verlag, 1982), p. 20.

embryo. Recent studies also suggest that the spatial pattern of expression of genes normally localized in the node, or "organizer," at the anterior of the primitive streak could be used as a molecular marker to signal the onset of gastrulation.[4]

At the end of gastrulation, about day 17 in vivo, the three germ layers of the embryo are in place. At this stage the cells are no longer pluripotent, but they are still multipotent; the cells of each layer give rise to a variety of tissue and organ types within a broad category. For example, cells of the ectoderm differentiate into cells of the epidermis and the nervous system, while cells of the mesoderm give rise to blood and muscle.[5]

Following gastrulation, the next stage of development involves the formation of the primitive nervous system. This first appears as a flat plate of cells (the neural plate), which then rolls up into a hollow tube. At the same time the anterior end of the tube becomes divided into several regions, which represent the future fore-, mid-, and hindbrain vesicles, while the remainder of the tube develops into the spinal cord. In vivo, neural development begins at about day 18, the neural tube begins to close at around 21 days, and neurulation is completed by the end of the fourth week (day 28).

Areas of Research

Many of the techniques presently used in IVF programs, or cited in proposals for future studies with preimplantation embryos, were originally developed in research with laboratory animals, in particular mice. Much valuable research is also being done with nonhuman primates—for example, on oocyte maturation, gamete interaction, and embryo-maternal interactions. In addition, over the past few years, there has been enormous progress in research with preimplantation embryos of domestic animals, including those of cow, sheep, and pig. In some experiments—for example, those designed to study the ability of nuclei from preimplantation embryos to support development of enucleated eggs—cow embryos have provided somewhat different results than mouse embryos. Nevertheless, it is now widely accepted in the scientific community that the basic principles of embryonic development, and in many cases even the genes regulating this development, are very similar in all vertebrates.

As knowledge about animal systems has increased, diverse areas of research aimed at understanding both the comparability and the uniqueness of human reproduction and development have opened up new scientific possibilities, many of which are described below.

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[4] See, for example, R.S.P. Beddington and J.C. Smith, "The control of vertebral gastrulation: Inducing signals and responding genes," *Current Opinion in Genetics and Development* 3:655-661, 1993.

[5] See K.L. Moore and T.V.N. Persaud, *The Developing Human: Clinically Oriented Embryology*, 5th ed. (Philadelphia: W.B. Saunders, 1993); H. Tuchmann-Duplessis, G. David, and P. Haegel, *Illustrated Human Embryology, Vol. 1: Embryogenesis* (New York: Springer Verlag, 1982).

Studies To Develop and Improve Clinical Protocols for the Treatment of Infertility

The procedure of IVF of human oocytes is now widely available in many countries throughout the world and in hundreds of centers in the United States. It was originally developed for the treatment of infertility that was due to blocked fallopian tubes but 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 preimplantation genetic diagnosis to enable fertile couples at risk for transmitting severe or fatal inherited diseases to have healthy children.

Although details of the IVF procedure vary among centers, the basic principles are as follows:[6] Oocyte donors are treated 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 and carries with it a low risk (less than 1 in 100) of an adverse reaction. Following completion of the hormone treatment, mature follicles are detected by sonography, and an average of around 10 are collected by transvaginal aspiration under sedation. The oocytes are then inseminated and cultured in sterile fluid for about 2 days. When they have reached the four- to eight-cell stage, between three and six embryos are transferred to the uterus, and untransferred embryos are usually frozen if they are developing normally.

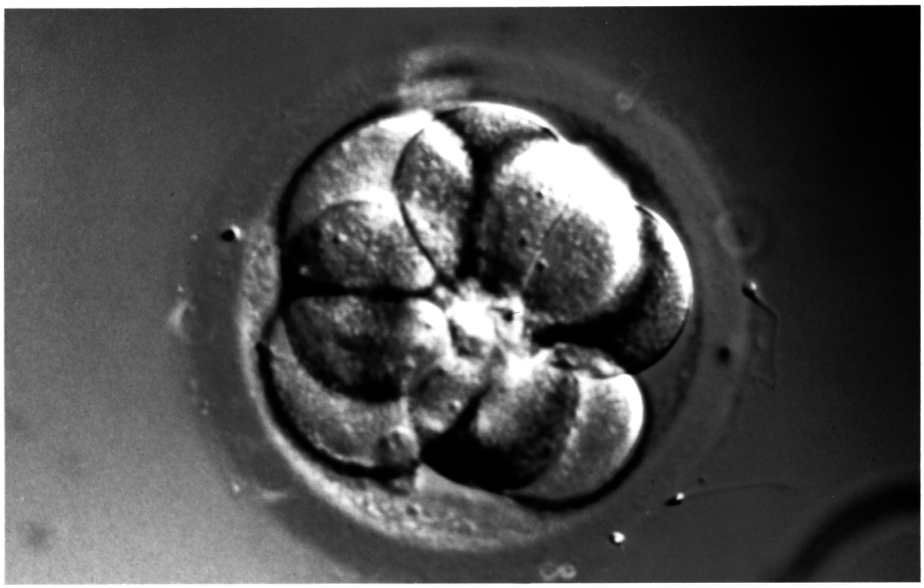

Figure 2. Human eight-cell embryo. (R.A. Pedersen)

Unfortunately, the efficiency of the IVF procedure is low, and only around 5 to 10 percent of fertilized eggs give rise to live-born children, depending on factors such as age of the recipient and

[6] P.R. Braude, "Fertilization of human oocytes and culture of human preimplantation embryos in vitro," in M. Monk (ed.), *Mammalian Development* (Oxford: IRL Press, 1987), pp. 281–306.

the reason for infertility.[7] Although implantation rates as high as 20 percent have been reported, the rate achieved by average IVF programs for younger patients is 10 percent. There is evidence that up to 70 percent of normally (in vivo) fertilized human embryos fail to result in a successful pregnancy, but even so the IVF rate is still low compared with unassisted reproduction.[8] There are many reasons for the failure of in vitro fertilized eggs to develop properly. Some of the oocytes do not fertilize at all, and some are fertilized by more than one sperm (polyspermy). Others stop dividing after reaching the two- to four-cell stage or later, and when allowed to remain in culture, only about 50 percent of fertilized eggs reach the blastocyst stage, which precedes the specialization events described above. Following transfer, some embryos fail to implant and others implant but die soon after, so that the pregnancy is not maintained.

To date, evidence suggests that some deficiencies causing failure lie in the oocytes themselves (intrinsic defects), while others result from suboptimal culture conditions or uterine environment (extrinsic defects). In some cases, the oocytes may be defective because they have developed chromosomal abnormalities during their long resting period in the ovary. In others, the rapid terminal maturation induced by hormonal hyperstimulation may cause the oocytes to be abnormal and either fail to fertilize or develop abnormally following fertilization.

The relative importance of intrinsic problems might be investigated by comparing oocytes matured in vitro from ovaries of women of different ages with oocytes collected from a donor after hormonal hyperstimulation. Attempts to improve extrinsic factors such as culture conditions have included the use of different media, the addition of different supplements, and the coculture of nonhuman embryos with cell lines from different species and tissues.[9] The rationale for the last approach is that the cell lines may produce rare growth factors or nutrients absent in standard media or may remove harmful agents (e.g., oxidants) that accumulate during culture. Improvements in culture conditions could be made if more information was available about gene expression in early human embryos. For example, if studies showed that cleavage-stage embryos express a gene encoding a growth factor receptor, then it would make sense to test the effect of adding the growth factor to the medium.[10] Other benefits might come from increased information about the biochemistry and metabolism of the early human embryo.

Another line of research that might improve clinical protocols is the development of noninvasive diagnostic tests for embryos with a high potential for implantation, based, for example, on the measurement of secretion of a protein into the medium or the rate of production of a particular

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[7] P.R. Braude, V.N. Bolton, M.H. Johnson, "The use of human pre-embryos for infertility research," in G. Bock and M. O'Connor (eds.), *Human Embryo Research: Yes or No?* (London: Tavistock Publications, 1986), pp. 63–82; J. Van Blerkom, "The History, Current Status and Future Direction of Research Involving Human Embryos," a paper prepared for the NIH Human Embryo Research Panel, January 10, 1994. (See volume II of this report.)

[8] R. Edwards, "Causes of early embryonic loss in human pregnancy," *Human Reproduction* 1:185, 1986.

[9] B. Bavister, "Response to the use of co-culture for embryo development," *Human Reproduction* 8:1160, 1993; A. Bongso, C. Fong, S. Ng, and S. Ratnam, "The search for improved in vitro systems should not be ignored: Embryo co-culture may be one of them," *Human Reproduction* 8:1155, 1993.

[10] A.J. Watson, P.H. Watson, M. Arcellana-Panilio, D. Warnes, S.K. Waler, G.A. Schults, D.T. Armstrong, and R.F. Seamark, "A growth factor phenotype map for ovine preimplantation development," *Biology of Reproduction* 50:725–733, 1994.

metabolite. This would allow fewer embryos to be transferred in each cycle and might reduce the risks of multiple births that accompany protocols in which more than three embryos are transferred. The Panel heard that the morphology of human cleavage-stage embryos is quite variable, and there appears to be little correlation between morphology and developmental potential.[11] In addition, some problems such as polyspermy, which normally leads to developmental arrest, may be corrected during early cleavage—for example, by elimination of one set of paternal chromosomes.

Other noninvasive diagnostic tests could be imagined, such as assays for fully mature oocytes or for blastocysts that are "implantation competent." Again, development of such tests would be facilitated by more information about the molecular characteristics of human oocytes and embryos.

Studies of Preimplantation Diagnosis of Genetic and Chromosomal Abnormalities

Over the past decade, the areas of gene discovery and molecular medicine have expanded exponentially, leading to the ability to diagnose genetic disease. For families with a high risk of genetic disease in their offspring (25 to 50 percent), there are currently few medical options for the most severe disorders. Many couples are unwilling to accept these high risks and elect to have no more children. Some families elect adoption. Still others will use artificial insemination, using the sperm of an anonymous male donor. For those who attempt pregnancy, conventional prenatal genetic testing via chorionic villus sampling (10 weeks gestation) or amniocentesis (16 weeks gestation) can provide answers regarding the genetic status of the fetus. If testing shows the fetus to be affected, the couple is then faced with the dilemma of what to do with that information based on the nature and severity of the genetic disease and on their ethical and religious convictions.

A new technology has been developed that provides another alternative for such couples. The technique, called preimplantation genetic diagnosis, combines the techniques of assisted reproduction and IVF with the molecular detection of gene mutations in a single cell (blastomere) derived from a cleavage-stage (eight-cell) embryo. Prior to uterine transfer of the IVF-generated embryo, a single cell is biopsied from the developing embryo at 3 days postfertilization, when it comprises about six to eight cells.[12] Embryos that do not have the genetic disease are then transferred to the woman's uterus. Couples seeking this approach are fertile but usually have previously conceived an affected child who is severely ill or has died of the condition. Some couples who are opposed to abortion of the fetus in the first or second trimester of pregnancy find this earlier diagnostic option more acceptable. In some cases, early diagnosis provides a medical and psychological benefit, because some affected fetuses cannot survive beyond the second trimester as the condition disrupts fetal development and causes repeated spontaneous miscarriages.

This approach to prenatal diagnosis, however, is still experimental. At this writing, 29 healthy children have been born and 11 pregnancies are ongoing worldwide from the application of

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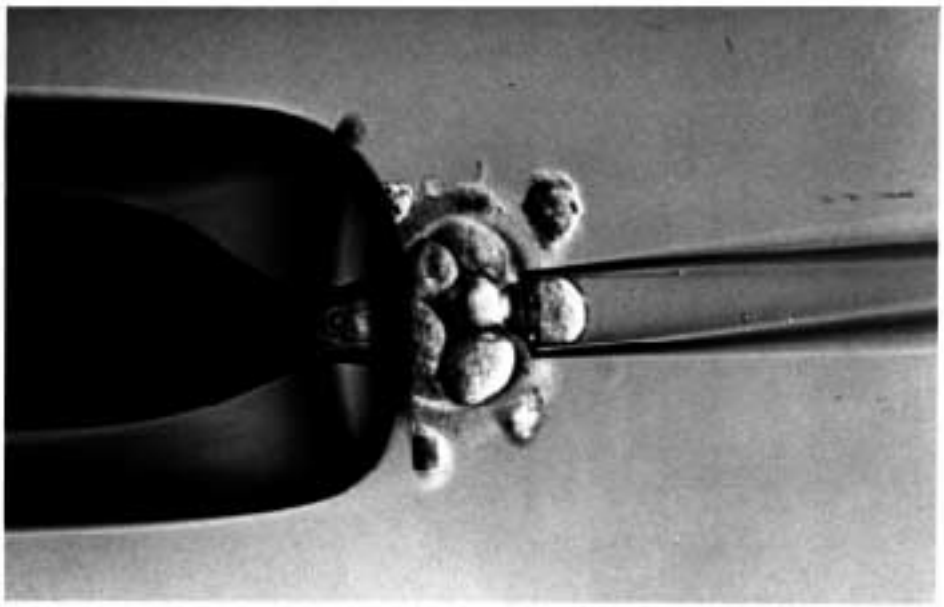
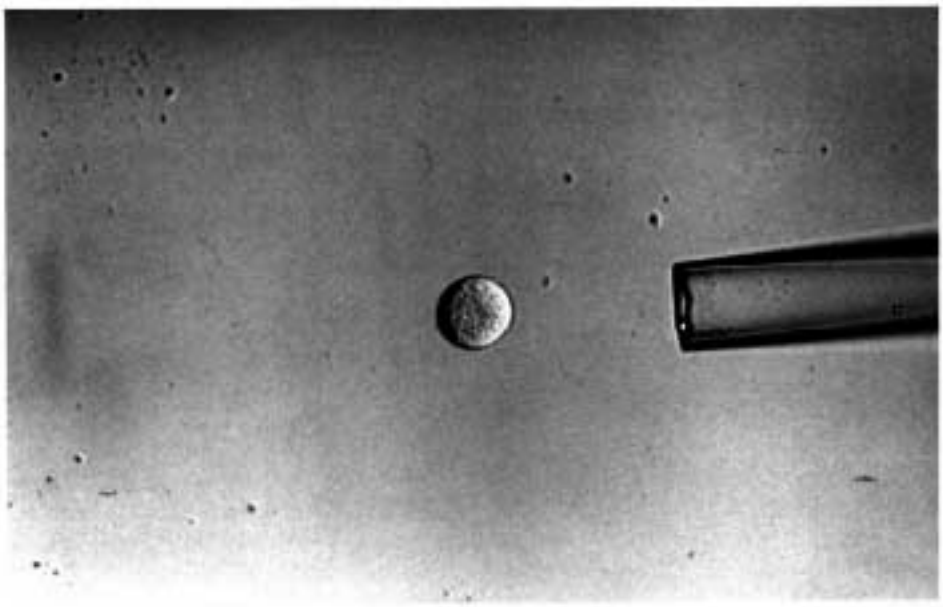
[11] J. Van Blerkom, "The History, Current Status and Future Direction of Research Involving Human Embryos," a paper prepared for the NIH Human Embryo Research Panel, January 10, 1994. (See volume II of this report.)

[12] Single-blastomere biopsy is not equivalent to cloning by blastomere splitting (see pages 28–30), since the cell is used immediately for DNA extraction and not cultured to form another embryo.



(a)



(b)

Figure 3. Biopsy of human embryo (a) during and (b) after. (R.A. Pedersen)

this new technology in families at high risk of having a child with a serious chromosomal or single-gene defect.[13] Among the diseases to which preimplantation diagnosis has been applied successfully are cystic fibrosis, Lesch-Nyhan syndrome, Duchenne muscular dystrophy, and Tay-Sachs disease. The technology has been used to assist couples who are at risk for transmitting X-linked recessive diseases such as X-linked mental retardation, hemophilia A, adrenoleukodystrophy, myotubular myopathy, and spastic paraplegia. Currently, couples are requesting enrollment into a clinical trial to study the overall safety and efficacy of this technology. Additional research is needed to improve and expand diagnostic testing in single cells; develop, evaluate, and compare the safety of various blastomere biopsy technologies; and begin a carefully controlled clinical trial to test the utility of this approach to prenatal diagnosis before pregnancy.

Studies of Morphology, Biochemical and Biophysical Properties, and Genetic Expression of Pregastrulation-Stage Embryos

Strong arguments can be made that more high-quality information about the human oocyte and preimplantation embryo would help to improve the outcome of clinical procedures such as those outlined in the previous sections. Much of this information could be obtained by applying modern techniques of molecular biology and biochemistry to scarce embryonic material. For example, it is now possible to assemble computerized databases of most of the proteins made by very small numbers of embryonic cells.[14] In addition, "cDNA libraries" can be generated that contain copies of all the genes expressed in small numbers of cells, or even individual cells, at different times during development (e.g., two-cell, four-cell, blastocyst, regions of the pre-primitive-streak-stage embryo).[15] These libraries are essentially "immortal" and could be distributed to many laboratories specialized in detecting specific classes of genes. Information from different laboratories could be pooled and shared, thus magnifying the impact of high-quality research with a small number of embryos or cells.

Studies on the Maturation, Fertilizability, and Developmental Potential of Oocytes, Including Cryopreservation of Unfertilized Oocytes

During the normal monthly female reproductive cycle, only a single egg is released from the ovary at the time of ovulation. This egg, also known as a mature oocyte or ovum, has had a long history. Unlike sperm, which are constantly replenished during the adult life of a man, all the eggs a woman will ever have are present in the ovary during fetal development. At this time, each small

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[13] Y. Verlinsky, "Current progress in pre-implantation genetic diagnosis," *Journal of Assisted Reproductive Genetics* 10:353–360, 1993. An updated report on this technology is forthcoming; see "International Working Group on Preimplantation Diagnosis," *Journal of Assisted Reproductive Genetics*, in press, 1994.

[14] K.E. Latham, J.I. Garrels, and D. Solter, "Two-dimensional gel analysis of protein synthesis," in *Methods in Embryology, Vol. 225: Guide to Techniques in Mouse Development* (New York: Academic Press, 1993), pp. 473–489.

[15] G. Brady and N.N. Iscove, "Construction of cDNA libraries from single cells," in *Methods in Enzymology, Vol. 225: Guide to Techniques in Mouse Development* (New York: Academic Press, 1993), pp. 611–623; J.L. Rothstein, D. Johnson, J. Jessee, J. Skowronski, J.A. DeLoia, D. Solter, and B.B. Knowles, "Construction of primary and subtracted cDNA libraries from early embryos," in *Methods in Enzymology, Vol. 225: Guide to Techniques in Mouse Development* (New York: Academic Press, 1993), pp. 587–610.

oocyte, of which there are hundreds of thousands, is surrounded by a group of nurse cells, which nourish the egg during its long process of growth and maturation. The tightly coordinated and interdependent unit of egg and nurse cells is known as a follicle. The development of follicles begins during late fetal life, but most of them, for reasons that are not yet understood, degenerate before they reach advanced stages. At the time of puberty, the remaining follicles begin to complete their development, and usually one mature egg, ready to be fertilized, is ovulated per month.[16]

During every normal cycle, the pituitary gland releases hormones that stimulate the maturation of a single oocyte and its release (ovulation) into the oviduct. The maturation process involves both the cytoplasm and the chromosomes of the oocyte. During cytoplasmic maturation, factors (proteins and RNA) are laid down and stored in the egg for activation during the first few cell divisions after fertilization. If these factors are defective in some way, the early embryo will not develop properly and will stop dividing. In fact, studies have shown that it is not until the four-cell stage that the human embryo starts to express its own genes and make its own proteins, rather than depend completely on those laid down during the development of the egg.[17]

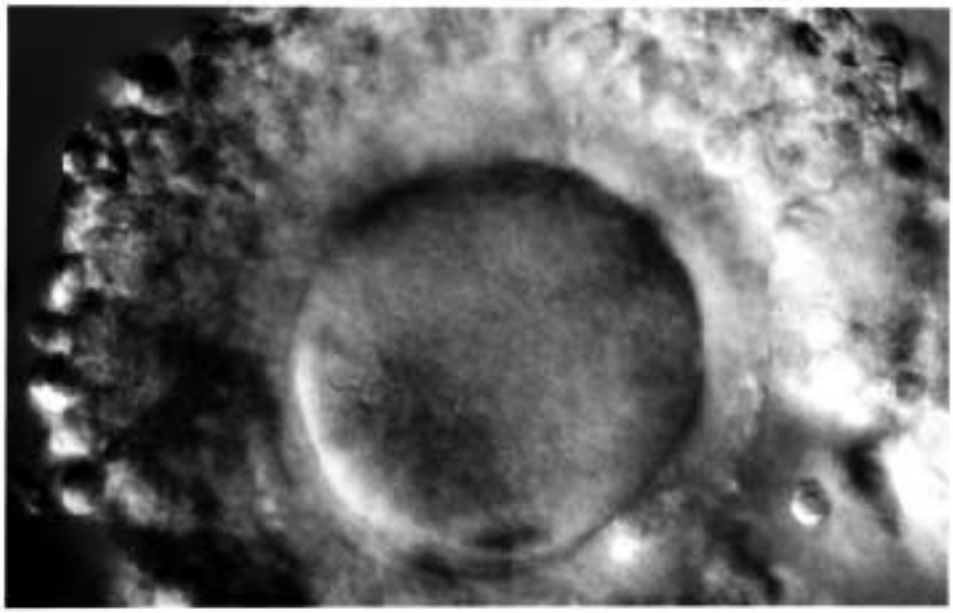

Figure 4. Human oocyte. (R.A. Pedersen)

Equally important to the viability of the fertilized egg and its ability to give rise to a normal embryo is the special process of chromosomal maturation and segregation, known as meiosis, that

[16] For a review of the process of egg maturation in vivo and in vitro, see R.G. Gosden, N.I. Boland, N. Spears, A.A. Murray, M. Chapman, J.C. Wade, N.I. Zhoday, and N. Brown, "The biology and technology of follicular oocyte development," *In Vitro Reproductive Medicine Reviews* 2:129–152, 1993.

[17] P.R. Braude, V.N. Bolton, and S. Moore, "Human gene expression first occurs between the four- and eight-cell stages of preimplantation development," *Nature* 332:459–461, 1988.

takes place during oocyte development. During its long residence in the ovary, which can last up to 40 or 50 years, the chromosomes of the egg are highly extended and intertwined. This makes the DNA and chromosome structure particularly vulnerable to environmental agents and toxic chemicals. As the final stages of oocyte development are reached in response to hormonal signals, the chromosomes begin to wind up and become coated with special proteins. At the actual time of ovulation, a complex process known as chromosome reduction takes place, which reduces the number of chromosomes in the oocyte from 46 (the diploid number) to 23 (the haploid number). This prepares the oocyte for fertilization by the sperm, which also contains 23 chromosomes. The fertilized egg then normally contains 23 chromosomes from the mother and 23 chromosomes from the father. If errors occur during the final oocyte maturation process, or the long period of development leading up to it, then the chromosomes may not segregate properly and too many or too few chromosomes may be present in the oocyte before fertilization. This leads to birth defects, such as Down's syndrome or trisomy 18, or failure to undergo embryonic development altogether.

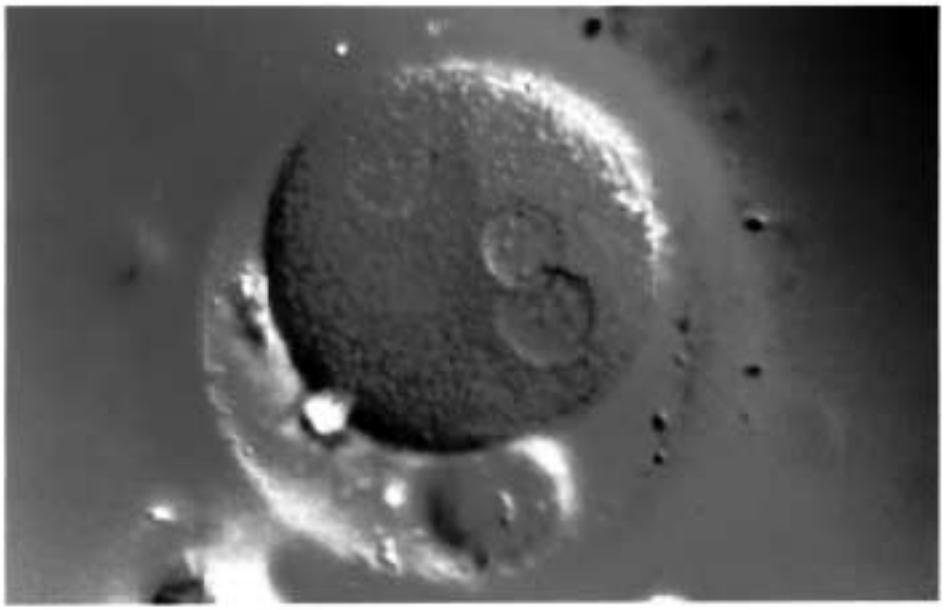

Figure 5. Fertilized human oocyte. (R.A. Pedersen)

Late-stage oocytes can be removed from large (antral) ovarian follicles before they receive the maturation-stimulating signal from the pituitary gland. With appropriate conditions, if they are cultured outside the body, these oocytes will mature as if they were still within the follicle. Studies using laboratory or farm animals have shown that these in vitro matured oocytes can be fertilized and will give rise to live-born, normal offspring if they are transferred to the uterus. Studies in South Korea[18] and Australia[19] have demonstrated that the same procedures can be carried out using

[18] K.Y. Cha, D.H. Choi, J.J. Koo, S.Y. Han, J.J. Ko, and T.K. Yoon, "Pregnancy after in vitro fertilization of human follicular oocytes collected from nonstimulated cycles, their culture in vitro, and their transfer in a donor oocyte program," *Fertility and Sterility* 55:109–113, 1991; K.Y. Cha, B.R. Do, H.J. Chi, T.K. Yoon, D.H. Choi, J.J. Koo, and J.J. Ko, "Viability of human follicular oocytes collected from unstimulated ovaries and matured and fertilized in vitro," *Reproduction, Fertility, and Development* 4:695–701, 1992.

human oocytes, but much more research is needed in this area before it becomes a routine clinical procedure. For example, the optimal culture conditions need to be determined for oocytes of different sizes and states of maturity.

In order to follow maturation or to compare the different culture procedures, it is necessary to assay whether maturation has been successful. This entails deliberately fertilizing the oocytes at the end of the culture period and allowing them to develop. Because the long-term aim is to use the oocyte maturation procedure therapeutically, the best test for successful maturation is to culture the embryos to the blastocyst stage. Not until this has been done successfully, in a highly reproducible way, could clinicians be confident that implantation would follow transfer of the embryos to the uterus.

As described previously, small immature oocytes develop slowly inside the ovary into large oocytes inside mature follicles. During this time, the oocytes undergo many changes. Not only do they become much larger, having stored valuable molecules for use during early embryo development, but they also change in other ways. For example, they produce a covering, known as the zona pellucida, that plays a critical role in allowing only one sperm to penetrate the egg at the time of fertilization. Studies with immature follicles taken from young mice have shown that it is possible to study the growth and development of immature oocytes in culture, and embryos produced from these oocytes have developed to healthy pups after transfer to the uterus.

If the in vitro oocyte maturation procedure is improved, there will be important clinical benefits in IVF programs. For example, infertile women and oocyte donors would not have to undergo hormonal hyperstimulation, which has a low, but real, risk associated with it. This risk is considerably higher in women suffering from infertility because of polycystic ovarian disease. In addition, many fertilizable oocytes could be obtained from ovaries donated by women undergoing elective gynecological surgical procedures without subjecting them to hormonal stimulation. Women confronting chemotherapy for cancers such as breast cancer could have eggs harvested at the time of diagnosis, without having to be stimulated. In addition, instead of an average of 10 mature eggs being retrieved after 2 weeks of hormonal stimulation, a small biopsy of the ovary could yield hundreds of immature eggs that could be stored for future potential childbearing.

In vitro maturation would have to be coupled to another important advance, namely, the improvement of freezing of unfertilized oocytes (cryopreservation). Some progress has already been made in freezing oocytes obtained from women with and without hormonal stimulation.[20] These oocytes can be recovered from storage and show a good rate of embryo development after fertilization, but more research is needed in this area to increase the efficiency and safety of the procedure and to determine whether it increases the risk of chromosomal abnormalities in embryos.

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[19] A. Trounson, C. Wood, and A. Kansche, "In vitro maturation and the fertilization and developmental competence of oocytes recovered from untreated polycystic ovarian patients," *Fertility and Sterility* 62:353-362, 1994.

[20] T.L. Toth, H.W. Jones, S.G. Baka, S. Muasher, L.L. Veeck, and S.E. Lanzendorf, "Fertilization and in vitro development of cryopreserved human prophase I oocytes," *Fertility and Sterility* 61:891-894, 1994; T.L. Toth, S.E. Lanzendorf, B.A. Sandow, L.L. Veeck, W.A. Hassen, K. Hansen, and G.D. Hodgen, "Cryopreservation of human prophase I oocytes collected from unstimulated follicles," *Fertility and Sterility* 61:1077-1082, 1994.

There is much to be learned about oocyte development from the earlier stages up to the time of final maturation and fertilization, using culture systems. Among the questions that could be addressed are the following: What are the nutritional requirements for normal oocyte development, and how do the oocyte and the follicle nurse cells interact with each other? What hormones and growth factors are important for follicle maturation, and why do some women run out of mature oocytes and so become infertile very early in life? What regulates the production of the proteins and RNA stored in oocytes, and what are their functions during early embryo development? How is the zona pellucida produced? Answering these questions would have many important applications. For example, it is likely that significant new information could be obtained regarding new approaches to contraception. In addition, there might be promising new strategies discovered for avoiding chromosomal damage by environmental agents during the long development of the oocytes. This would reduce the frequency of birth defects and infertility that are related to the production of defective oocytes. Finally, a case could be made for comparing the properties and developmental potential of oocytes matured from fetal, neonatal, and adult ovaries. Unlike oocytes from fetal and neonatal ovaries, oocytes from adult women will have been exposed to environmental agents and, in some documented cases, to specific drugs or toxic chemicals during their long maturation. They are therefore more likely to show the chromosomal abnormalities that affect development.

Studies of the Process of Fertilization

The first stage of fertilization involves interaction of the sperm with the egg, leading to the fusion of the membranes surrounding the two gametes and the entry of the sperm nucleus into the egg cytoplasm. Changes rapidly occur in the egg membrane so that it normally cannot be penetrated by a second sperm. In the mouse, there has been considerable progress in understanding the molecular mechanisms underlying these different processes. For example, it is now known that the membrane around the sperm head contains specific proteins, or ligands, that interact with specific receptors in the egg membrane. In one study, it was reported that the sperm proteins come as pairs, one member binding to the egg receptor and the other promoting fusion of the membranes.[21]

Research has shown that the egg and sperm proteins involved in fertilization are related to families of proteins on other cells and tissues in the body that are involved in completely different kinds of interactions. For example, platelets that aggregate during blood clotting use proteins known as "integrins" that belong to the same family of proteins known as egg receptors. Certain pathogenic viruses fuse with cells using proteins related to the fusion proteins in the sperm membrane. Therefore, there is nothing scientifically unique about the interaction between the egg and sperm. However, there are likely to be some differences in the structure of the ligands and receptors between humans and other species, so that animal studies could not be translated directly to the human. One benefit of studies on the molecular basis of fertilization might be a better understanding of why some oocytes fail to fertilize, while others are fertilized by more than one sperm.

[21] For a review, see C. Damsky, A. Sutherland, and S. Fisher, "Extracellular matrix 5: Adhesive interactions in early mammalian embryogenesis, implantation, and placentation," *The FASEB Journal* 7:1320-1329, 1993.

Studies of New Contraceptives

Another likely application of studies on the mechanisms of fertilization would be the development of new contraceptives.[22] These contraceptives could involve the use of vaccines to raise antibodies in women against proteins on the surface of the egg or sperm. Alternatively, small soluble peptides could be used to interfere with the binding of membrane-bound sperm ligands and egg receptors. In order to test new contraceptives designed on the basis of interference with the interaction of the egg and sperm, it would be necessary to set up in vitro assays that would involve successful fertilization of the control sample. The best end point would probably be the appearance of two pronuclei in the cytoplasm of the control (fertilized) eggs.

Studies of Parthenogenesis

Parthenogenesis is the process of egg development without fertilization. It is important to differentiate between "spontaneous" and "induced" parthenogenesis. "Spontaneous" parthenogenesis simply means that it occurs as a natural event or process. This does not happen very often in mammals, although it occurs quite frequently in some nonmammalian species. Although spontaneous parthenogenesis does not happen often in mammals, a certain type of ovarian tumor called a "teratoma" or "dermoid cyst" originates from eggs that develop parthenogenetically while still in the ovary. Although ovarian teratomas in women are usually benign, they are sometimes malignant when they occur before puberty or in young women. It is important, therefore, to study the problems that occur during oocyte development that promote this atypical parthenogenetic activation.

"Induced" parthenogenesis means that some treatment was done to stimulate the process. For example, parthenogenesis can be induced rather easily in some mammalian species, such as the mouse and rabbit, by treatment with certain chemicals or by electrostimulation. It is much more difficult to induce parthenogenesis of human eggs,[23] although experimentation might produce more efficient methods.

It has been shown using laboratory animals that most induced or spontaneous mammalian parthenogenetic embryos (which are known as parthenogenones or parthenotes) can develop like normal embryos to the blastocyst stage, although they do so somewhat more slowly. After this stage, most of them degenerate and die.[24] The minority of mammalian parthenotes that do proceed beyond implantation are very small in size and do not reach an advanced stage before they die. Thus, there is a profound and intrinsic biological barrier that prevents mammalian parthenotes from developing to advanced fetal stages or being born. Studies have shown that this biological barrier is due to a process known as "DNA imprinting." Parts of the chromosomes from the mother (egg) and from the

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[22] R.J. Aitken and D.W. Lincoln, "Human embryo research: The case for contraception," in G. Bock and M. O'Connor (eds.), *Human Embryo Research: Yes or No?* (London: Tavistock Publications, 1986), pp. 122–140.

[23] N. Winston, P. Braude, S. Pickering, M. George, A. Cant, J. Currie, and M. Johnson, "The incidence of abnormal morphology and nucleocytoplasmic ratios in 2-, 3-, and 5-day human pre-embryos," *Human Reproduction* 6:17, 1991.

[24] M.A. Surani, R. Kothary, N.D. Allen, P.B. Singh, R. Fundele, A.C. Ferguson-Smith, and S.C. Barton, "Genome imprinting and development in the mouse," in M. Monk and A. Surani (eds.), *Genomic Imprinting: Development* (Suppl.), pp. 89–98, 1990.

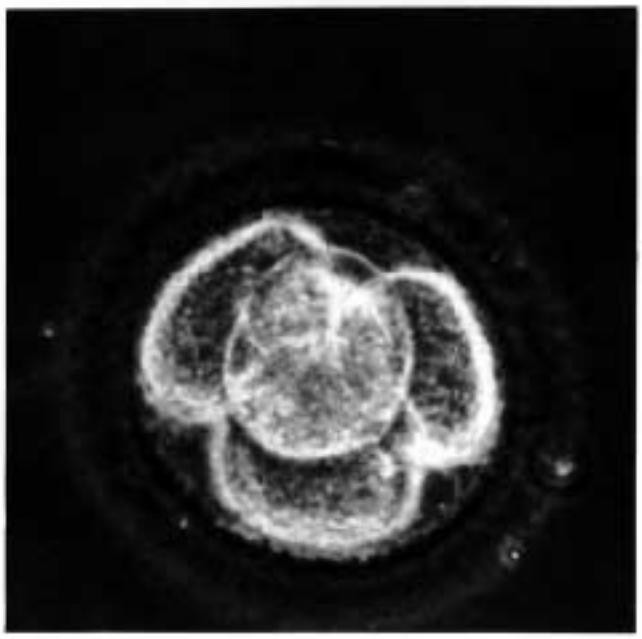

Figure 6. Four-cell parthenote. (*The Biochemist* 16(2):April/May 1994)

father (sperm) are "marked" in a special way that makes it necessary that chromosomes from both sexes be present in the same embryo for development to proceed normally.[25] In the case of parthenotes, the chromosomes from the sperm are absent.

In another kind of embryo, known as an androgenote, in which the chromosomes only come from the sperm, development also fails around the time of implantation. If the androgenetic embryos do implant, they have a tendency to give rise to benign trophoblast tumors known as "hydatidiform moles" and these may progress to highly malignant choriocarcinoma. These conditions occur naturally and are seen in clinical medicine but have not been studied well enough to understand their mechanism of formation.

The technology for the parthenogenetic activation of human eggs is not as well established or as successful as it is in laboratory or domestic animals. However, there has not been much effort in this area of research, and there is every reason to believe that further studies would be fruitful. If this were achieved, then human parthenotes might be a more acceptable alternative to deliberately fertilized oocytes for studying preimplantation development. Unlike fertilized eggs, they do not have a unique genetic constitution but only contain genetic material derived from the egg. Moreover, they do not have the potential for developing into a fetus.

Although mouse parthenotes do not develop to advanced stages, recent studies suggest that at least up to the blastocyst stage they express many of the same genes and proteins as normal embryos and are very similar in their metabolic behavior and biochemical characteristics. If human parthenotes are as similar to normal human embryos as mice parthenotes are to those of mice, then human

[25] C. Ezzell, "Genomic imprinting and cancer," *Journal of NIH Research* 6:53–59, 1994.

parthenotes might be useful for research as models of the human preimplantation embryo. Apart from being a possible substitute for normal embryos, human parthenotes, and also embryos in which only paternal chromosomes are present, have scientific interest in their own right. Studies on them might help explain the process of "genomic imprinting" and how it affects the expression of the particular genes needed for normal development beyond the blastocyst stage. It is now known that certain rare cancers in children are associated with the ablation of the imprinting signal or mark on specific genes. The abnormal inheritance of two copies of a chromosome or part of a chromosome from one parent is also associated with certain cancers (e.g., hydatidiform mole/choriocarcinoma and cancers in children with Beckwith-Wiedeman syndrome) and with profound abnormalities in postnatal development.[26] Studies on gene imprinting are being carried out vigorously in mice and other experimental animals, and more basic work needs to be done.

Studies of Uterine Implantation, Maternal-Fetal Interactions, and X Inactivation in Extraembryonic Tissues

During the complex process known as implantation, the blastocyst attaches to the lining of the uterus, moves into the underlying stroma, establishes a secure placental connection with the mother, and avoids being rejected as foreign tissue. All these steps are crucial to the normal development of a healthy infant; studies have suggested that some pregnancy failure, including early spontaneous miscarriage, occurs in the human around the time of implantation or is the result of suboptimal growth of the placenta and its interaction with the uterus. In spite of the importance of implantation, surprisingly little is known, either in humans or in laboratory animals, about the mechanisms underlying the different processes involved.

There is evidence for special attachment, or adhesive, proteins, known as "integrins," on the surface of the trophectoderm cells that constitute the outer layer of the blastocyst.[27] These proteins probably interact with ligand molecules in the uterus, either on the epithelial cells or in the stromal layer immediately underneath. In addition, studies have identified a number of different protein growth factors and their receptors that are made either by the trophectoderm cells, which give rise to a large part of the placenta, or by the uterus.[28] These growth factors appear to be involved in the interaction between the embryo and the maternal tissue. Mutations in the genes encoding some of these factors have been shown to result in decreased fertility in mice.[29]

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[26] W. Reik, "Genomic imprinting and genetic disorders in man," *Trends in Genetics* 5:331–336, 1989; C. Ezzell, "Genomic imprinting and cancer," *Journal of NIH Research* 6:53–59, 1994.

[27] A.E. Sutherland, P.G. Calarco, and C.H. Damsky, "Developmental regulation of integrin expression at the time of implantation in the mouse embryo," *Development* 119:1175–1186, 1993.

[28] L.J. Regenstreif and J. Rossant, "Expression of the c-fms proto-oncogene and of the cytokine, CSF–1, during mouse embryogenesis," *Developmental Biology* 133:284–294, 1989.

[29] J.W. Pollard, J.S. Hunt, W. Wiktor-Jedrzejczak, and E.R. Stanley, "A pregnancy defect in the osteopetrotic (op/op) mouse demonstrates the requirement for CSF–1 in female fertility," *Developmental Biology* 148:273–283, 1991.

Studies with human blastocysts would show whether the surface adhesive proteins and the growth factors and receptors identified as important for mouse implantation are made by the human embryo at the same stage in development as in the mouse. This could be done by using standard biochemical assays for specific proteins or by analyzing cDNA library databases as described previously. Identification of these human proteins and the production of reagents specific for them might make it possible to develop noninvasive diagnostic tests for blastocysts that are ready to implant, or implantation competent, and so increase the efficiency of IVF programs, while avoiding the risks of multiple gestations.

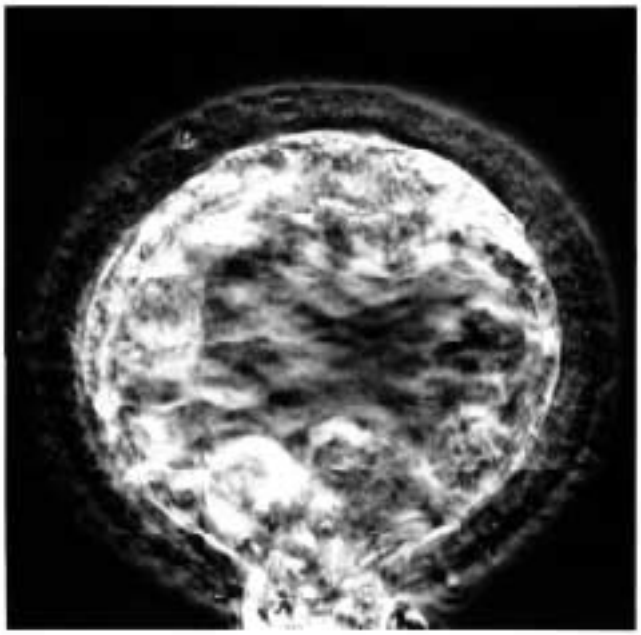

Figure 7. Human blastocyst-stage embryo (at 6 days), hatching spontaneously through zona pellucida.
(*The Biochemist* 16(2):April/May 1994)

It would also be possible to set up culture systems that mimic the process of blastocyst attachment and implantation into the lining of the uterus. This has been achieved with mouse blastocysts, using culture dishes on which a thin layer of uterine cells is growing. The trophoblast cells spread out over the surface of the dish and interact with the uterine cells in a specific way. One potential benefit of such research would be the identification of new contraceptives such as antibodies or peptides that would prevent the attachment of the blastocyst to the uterine lining. Another benefit would be increased understanding of the way in which trophectoderm and other placental cells invade the uterine lining and the underlying stroma but do not penetrate beyond the confines of the uterus. This has relevance to the abnormal process of tumor metastasis, in which cancer cells spread throughout the body by invading tissues and blood vessels.

In all mammals, one of the two X chromosomes present in the female is inactivated during normal development. Extensive studies in mice have shown that in the tissues of the placenta, including the cells of the trophectoderm lineage, the X chromosome inherited from the father is preferentially inactivated, while the X chromosome from the mother remains active. In contrast, in

the cells giving rise to the fetus, X inactivation is random. However, preferential paternal X inactivation has not been seen in human placental trophoblast cells, either taken during the first trimester or at term. The significance of this species difference is not clear, and it highlights the possibility that not all important developmental mechanisms are necessarily the same between the embryos of laboratory animals and humans. The process of X inactivation in human embryos therefore needs to be investigated further—for example, by studying its timing and specificity in cells isolated from the human preimplantation blastocyst.

Studies of Early Embryo Development Up to Gastrulation

Studies involving the culture of implantation stage mouse embryos always start with blastocysts that have been flushed from the uterus, so that the embryos have undergone optimal development before the culture begins.[30] The blastocysts are placed in culture so that the trophectoderm attaches and spreads out on a surface. The inner cell mass remains as a coherent group of cells, but the cells usually grow slowly and in a disorganized way, so that even under the best conditions only a few percent proceed to the gastrulation stage of development.[31] Once the embryo begins to establish a circulatory system, profound difficulties arise in maintaining normal development, and there are no published reports of this having been achieved with mouse embryos from the blastocyst stage, let alone from the fertilized egg. Moreover, it is impossible to place into the uterus mouse embryos that have been cultured in vitro beyond the implantation stage since the normal interaction of the placental tissue with the uterus is completely disrupted and cannot be restored after transfer.

The process of gastrulation is of fundamental importance to the development of all vertebrate embryos and is the focus of considerable research with frogs, fish, chickens, and mice to understand how the basic body plan of the embryo is set up and affected by environmental and genetic factors. Evidence suggests that the genes regulating gastrulation have been tightly conserved during evolution and work through very similar mechanisms in all vertebrates.[32] Before gastrulation is initiated, the embryo essentially has no craniocaudal (head-to-tail) or left-right axis and no organizing center directing the coherent establishment of form (morphogenesis). In the human embryo, a single organizing center, or node, appears for the first time as a small aggregation of cells near the edge of the embryonic disk at about 14 days after fertilization.[33] The node marks one end of the primitive streak, which is a line of cells determining the future midline of the embryo.

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[30] For a review of in vitro culture of mouse embryos, see D.A.T. New, in A.J. Copp and D.L. Cockcroft (eds.), *Postimplantation Mammalian Embryos* (New York: Oxford University Press, 1990), pp. 1–14.

[31] L.T. Chen and Y.C. Hsu, "Development of mouse embryos in vitro: Preimplantation to the limb bud stage," *Science* 218:66–68, 1982.

[32] For a review, see R.S.P. Beddington and J.C. Smith, "The control of vertebral gastrulation: Inducing signals and responding genes," *Current Opinion in Genetics and Development* 3:655–661, 1993.

[33] K.L. Moore and T.V.N. Persaud, *The Developing Human: Clinically Oriented Embryology*, 5th ed. (Philadelphia: W.B. Saunders, 1993); H. Tuchmann-Duplessis, G. David, and P. Haegel, *Illustrated Human Embryology, Vol. 1: Embryogenesis* (New York: Springer Verlag, 1982).

Cells in the embryonic disk (which is less than 1 mm in diameter at this time) move toward the primitive streak and node and then migrate through it, to form a new embryonic cell layer that will eventually give rise to most of the tissues of the body. The anterior end of the primitive streak marks the position of the future head, but primitive neural tissue does not appear until a few days after the beginning of gastrulation. The formation of the first blood cells also begins around the time of gastrulation. It is possible that lines of cells could be derived in culture from both the primitive neural and blood tissue that could be used after further differentiation for transplantation.

The node and primitive streak have a very characteristic morphology, and it is likely that they would become visible under the microscope in a few human embryos cultured under optimal conditions from the blastocyst stage. However, experience with cultured mouse embryos shows that the embryos develop more slowly in vitro than in utero, so that the primitive streak may not develop until after 14 days. Since gastrulation has been conserved throughout vertebrate evolution, it is very likely that genes that are expressed specifically in the node and primitive streak in mouse, chicken, and frog would be expressed in the same localized regions in human embryos.[34] These genes could be used as molecular markers to follow the appearance of the node and the effect of different culture conditions on embryo development and organization. However, in contrast to observing morphology alone, the determination of gene expression would require the scientist to fix (and thus destroy) the embryo, at least with today's technology.[35]

As described above, gastrulation is the first process in development that sets up the future body plan of the embryo, namely the position of the future head and tail and the relation of the different body parts to each other. If genetic problems, chromosomal imbalances, nutritional deficiencies (e.g., folic acid), or environmental teratogens are present at this time, the embryo either miscarries or gives rise to a newborn with profound developmental problems such as anencephaly or spina bifida. In order to understand how such problems arise, much more research on laboratory animals is necessary. However, in the long term, it will be important to know whether the same genes and developmental mechanisms are involved in human embryos. It would be very difficult to recover an embryo at the crucial gastrulation stage after a miscarriage or induced abortion because of its extremely small size and fragility. Therefore, in vitro culture combined with techniques such as cell biopsy and cDNA and protein analysis may be the only way of obtaining this information.

Research on Neurulation

The embryonic nervous system first appears around 18 days after fertilization as a flat plate of ectodermal cells (the neural plate) that then rolls up into a hollow tube (neurulation). The process of neurulation is one that may go wrong during development, giving rise to conditions such as cranio-rachischisis, or clefting, in which the brain and spinal cord are completely exposed (neural tube defects). Severe malformations in the early patterning of the anterior nervous system can give rise to anencephaly (absence of a brain), microcephaly (abnormally small head size), or holoprosencephaly

[34] R.S.P. Beddington and J.C. Smith, " The control of vertebral gastrulation: Inducing signals and responding genes," *Current Opinion in Genetics and Development* 3:655-661, 1993.

[35] See K.L. Moore and T.V.N. Persaud, *The Developing Human: Clinically Oriented Embryology*, 5th ed. (Philadelphia: W.B. Saunders, 1993); H. Tuchmann-Duplessis, G. David, and P. Haegel, *Illustrated Human Embryology, Vol. 1: Embryogenesis* (New York: Springer Verlag, 1982).

(midline facial clefting). These conditions usually lead to early fetal or neonatal death or spontaneous abortion.

Research into the mechanisms by which the neural plate closes and becomes divided into different regions and the genetic and environmental factors affecting very early neural development is currently being conducted extensively in animal model systems. Until the neural tube has closed and the anterior swellings have formed, the neural tissue is extremely primitive and special centers and nerve cell connections associated with brain function have not formed. In the long term, it might be important to investigate limited aspects of very early neural development (before the beginning of neural tube closure) in the human to understand the origin of severe developmental defects that cannot be studied using animals.

Isolation of Pluripotent Cell Lines From Human Blastocysts

Well-established methods are now available for obtaining continuous, or "immortal" (self-renewing), lines of undifferentiated stem cells, known as embryonic stem (ES) cells, from mouse blastocysts in culture.[36] The blastocysts are allowed to attach to the culture dish so that the trophoblast cells spread out, but the undifferentiated inner cells (the inner cell mass, or ICM) continue to grow as a tight, but unorganized, cluster. However, before the ICM can develop into the equivalent of the embryonic disk it is drawn up into a fine pipet, dissociated into single cells, and dispersed into another dish with a rich culture medium. Under these circumstances, the dissociated cells continue to grow rapidly and indefinitely. They 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 blastocyst, they can intermingle with the host ICM and take part in normal development, eventually contributing to all the tissues of the adult mouse, including nerve, blood, skin, bone, and germ cells. In other words, they are still "pluripotent," which indicates that the ES cells have not lost the capacity to give rise to specialized tissues, but they will not do so unless placed in the right environment. It should be noted that introducing human ES cells into a blastocyst would result in the making of a human-human chimera, a procedure that the Panel recommends be proscribed for Federal funding (this and other proscribed areas are discussed later in this and subsequent chapters of this report).

As long as the ES cells in culture are growing rapidly and are kept in a rich medium, they remain undifferentiated and can be maintained in this state indefinitely. However, if their growth slows down, they do differentiate, but in a disorganized and chaotic way, giving rise to primitive precursors of tissues such as blood, nerve, skin, and cartilage.[37] It is very likely that in the near future scientists will be able to use purified growth factors or related molecules to regulate this differentiation in a very controlled way and find conditions in which all the stem cells will turn into

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[36] See, for example, E.J. Robertson (ed.), *Teratocarcinomas and Embryonic Stem Cells* (Oxford: IRL Press, 1987).

[37] E.J. Robertson (ed.), *Teratocarcinomas and Embryonic Stem Cells* (Oxford: IRL Press, 1987); T.C. Doetschman, H. Eistetter, M. Katz, W. Schmit, and R. Kemler, "The in vitro development of blastocyst-derived embryonic stem cell lines: Formation of visceral yolk sac, blood islands and myocardium," *Journal of Embryology Experimental Morphology* 87:27-45, 1987.

blood precursors or into primitive nerve cells.[38] There is every reason to believe that such differentiated cells could be used for tissue transplantation, for example, to repair regions of the nervous system that have undergone damage (e.g., motor neurons in spinal cord injury) or degeneration (e.g., as in Parkinson's disease) or for bone marrow transplantation. Only differentiated cells, or cells of very limited developmental potential, would be used in such transplantation studies. Pluripotential stem cells with any risk of entering the germ line would be excluded by rigorous purification procedures before transfer. In any case, there is no evidence that ES cells injected into an adult mouse are able to enter the gonads and form gametes.

If human ES cell lines could be obtained from blastocysts, they would have enormous potential in many clinical fields and the long-term impact would be very high. A bank of ES cells could be established to overcome problems of matching tissue types, and each line could be used as a self-renewing resource to generate stem cells for such tissue as blood, nerves, and bone. Moreover, it might be possible to devise ways to avoid using large numbers of fertilized embryos for this purpose, for example, by using parthenogenetic blastocysts derived from activated but unfertilized eggs or by using the technique of nuclear transplantation to replace the nucleus in one ES cell line with a nucleus from the adult patient. By following this procedure, there would be no immune rejection of the donated cells, because the ES cell line would have the same genotype and therefore the same histocompatibility antigens as the person who receives them.

Studies of Choriocarcinoma and Metastasis

The relevance of studies on trophoblast invasion into the uterus to the problem of cancer metastasis has been previously discussed. Studies of chromosome abnormalities manifest during preimplantation development are also relevant to the origin of cancers of trophoblast tissue per se. Benign trophoblast tumors are known as hydatidiform moles, which consist of a mass of chorionic villi and either no fetus or a very abnormal one. Studies have shown that moles that have no fetus carry two, three, or even four sets of paternal chromosomes but no maternal chromosomes. It is thought that moles with two sets of paternal chromosomes arise from eggs fertilized by one diploid or two haploid sperm or by one haploid sperm that subsequently becomes diploid.[39] In either case, the maternal chromosomes are lost sometime during preimplantation development. Hydatidiform moles with paternal diploid chromosomes have a higher frequency than normal trophoblast tissue of giving rise to malignant, invasive tumors known as choriocarcinomas, but the reason for this predisposition is not known. While hydatidiform moles and resulting choriocarcinomas are rare, they are clearly one of a whole spectrum of clinical problems arising from chromosomal abnormalities manifest in the human preimplantation embryo.

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[38] Preliminary studies have shown progress in the development of blood precursors from mouse embryonic stem cells. See R.M. Schmitt, E. Bruyns, and H.R. Snodgrass, "Hemopoietic development of embryonic stem cells in vitro: Cytokine and receptor gene expression," *Genes and Development* 5:728–740, 1991; A. Miller and E. Dzierzak, "ES cells as a model of embryonic hematopoiesis," *Seminars in Developmental Biology* 4:341–349, 1994; T. Nakano, H. Kodama, and T. Honjo, "Generation of lymphohematopoietic cells from embryonic stem cells in culture," *Science* 265, 1098–1101, 1994.

[39] S.D. Lawler and R.A. Fisher, "The contribution of the paternal genome: Hydatidiform mole and choriocarcinoma," in C.W.G. Redman, I.L. Sargent, and P.M. Starkey (eds.), *The Human Placenta* (Oxford: Blackwell Scientific Publications, 1993), pp. 82–112.

Cloning

Three techniques have been used for producing genetically identical copies, or clones, of a single mammalian embryo. They are all called cloning despite significant differences in the methods used.[40] The first technique, known as blastomere separation, involves removing the zona pellucida from around a two- to eight-cell embryo (known as a morula), incubating it in calcium-free and magnesium-free saline so that the blastomeres separate and fall apart and then culturing the cells individually. Once the cells have divided a few times, they spontaneously form smaller-than-normal embryos, which can be transferred to the uterus. It should be noted that this technique is different from the technique of blastomere biopsy used in preimplantation genetic diagnosis. In the latter case, only one, or at the most two, blastomeres are collected and used immediately for DNA isolation; they are not cultured with the aim of producing additional embryos.

In the second cloning method, known as blastocyst division or induced twinning, a single embryo at the blastocyst stage is mechanically divided into two so that each part receives an approximately equal number of trophoblast and ICM cells. Each blastocyst is then transferred to the uterus, so that, at the most, one embryo gives rise to identical twins.[41]

The third method for cloning, nuclear transplantation, involves transferring a nucleus from a four- to eight-cell or later-stage embryo into the cytoplasm of an egg from which the genetic material has been removed. For example, if all four nuclei are transferred from a four-cell embryo into four enucleated eggs, then the genome will be quadruplicated. Contrary to popular ideas, this is not achieved by injecting an isolated nucleus, but by placing a single blastomere next to the enucleated egg and fusing the two membranes together artificially. The nucleus from the smaller blastomere then enters the larger egg cytoplasm and directs the development of the embryo.

Cloning by Blastomere Splitting or Dividing Blastocysts (Induced Twinning). The Panel was aware that cloning by these techniques has been advocated as a clinical procedure, for example, to (1) increase the chance of pregnancy for an infertile couple from whom only a few fertilized eggs are recovered; (2) minimize the number of subsequent egg retrievals and the attendant risks should the first transfer fail; and (3) improve the efficiency of preimplantation genetic diagnosis.[42]

Advocates of the first two applications appear to base their argument on the premise that returning two or four identical embryos will increase the chances of pregnancy substantially—intuitively, by two or four times. However, extensive animal studies have shown that this premise is false and that the inherent viability of embryos from separated blastomeres is reduced compared with that of unmanipulated, intact embryos, even if the separated blastomeres had developed into apparently healthy-looking blastocysts in culture. This reduced potential of separated blastomeres is not due to deficiencies in the cloning procedure but rather to the working of an intrinsic developmental program in the embryo that cannot be altered. In the case of sheep and cows, the best

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[40] Popular notions of cloning derive from science fiction books and films that have more to do with cultural fantasies than actual scientific experiments.

[41] S.M. Willadsen, "Cloning of sheep and cow embryos," *Genome* 31:956–962, 1989.

[42] See, for example, J.B. Massey, M.J. Tucker, H.J. Malter, and J.L. Hall, "Blastomere separation: Potential for human investigation," *Assisted Reproduction Reviews* 4:50–59, 1994.

pregnancy results with blastomere splitting are obtained with half embryos, i.e., either a two-cell embryo divided into two or a four-cell embryo divided into two two-cell embryos. Even so, the overall pregnancy rate is only increased by 30 to 50 percent.[43] Somewhat better results are obtained by separating a blastocyst into two halves, but the pregnancy rate is not doubled.

Application of cloning technology in the clinical setting would not be straightforward. First, in the case of blastocyst division, it is not easy to obtain human blastocysts, either in culture or by uterine flushing. Second, in the case of blastomere splitting, there is no reliable diagnostic test for distinguishing embryos with a high developmental potential from those with a low developmental potential, so that blastomere separation, even at the two-cell stage, might further reduce the viability of already compromised embryos. The freezing of embryos, as would be required to minimize the number of egg retrievals, is likely to even further reduce overall viability. For these and other reasons, it has been argued on scientific grounds that only very modest gains, if any, might be expected from applying blastomere or blastocyst splitting techniques to the clinical treatment of infertility at the present time.[44] The hopes of infertile couples might therefore be raised without due justification. In terms of the third clinical application, preimplantation genetic diagnosis, there is little scientific evidence that the supply of DNA is the rate-limiting factor in the overall efficiency of this procedure.

On the other hand, blastomere separation may be a useful method for generating populations of genetically identical embryos for certain scientific studies that do not involve transfer of the embryos to the uterus. For example, since humans are genetically very heterogeneous, arguments could be made for comparing the effect of different conditions on genetically identical embryos.

Cloning by Nuclear Transplantation. Nuclear transplantation techniques were first developed in the mouse, and they initially suggested that normal development was not possible when an enucleated egg received a nucleus from an older embryo. However, more recent experiments suggest that development may occur if the donated nucleus is transferred at a particular stage of the cell cycle.[45] Extensive studies have been conducted with domestic animals, in particular sheep and cows, showing limited success in cloning by this method. For example, in cows, nuclei have been transferred from morula and blastocyst-stage embryos into parthenogenetically activated (unfertilized) enucleated eggs. Following cleavage and implantation these embryos have developed into viable newborn calves. However, in a significant number of cases (20 to 30 percent) the calves show

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[43] S.M. Willadsen, "The developmental capacity of blastomeres from 4- and 8-cell sheep embryos," *Journal of Embryology and Experimental Morphology* 65:165–172, 1981; S.M. Willadsen, "Cloning of sheep and cow embryos," *Genome* 31:956–962, 1989; H.W. Jones, R.G. Edwards, and G.E. Seidel, "On attempts at cloning in the human," *Fertility and Sterility* 61:423–426, 1994.

[44] H.W. Jones, R.G. Edwards, and G.E. Seidel, "On attempts at cloning in the human," *Fertility and Sterility* 61:423–426, 1994.

[45] H.-T. Cheong, Y. Takahashi, and H. Kanagawa, "Birth of mice after transplantation of early cell-cycle-stage embryonic nuclei into enucleated oocytes," *Biology of Reproduction* 48:958–963, 1993.

nongenetic abnormalities, some of which persist after birth.[46] The reason for the birth defects is not yet known.

One possible application of nuclear transplantation with human embryos that does not involve cloning is the correction of maternally inherited cytoplasmic defects, for example, in mitochondria. The mitochondrion is a kind of power generator or battery in the cell, and there are hundreds of thousands of them. They make the energy source known as adenosine triphosphate from glucose and also many other byproducts that are used by the cell to make more complex molecules. Each mitochondrion has a small amount of DNA that is circular and replicates each time the mitochondrion multiplies. All the mitochondria in an egg come from the mother, so that genetic defects in mitochondrial DNA are maternally inherited from generation to generation by all the embryos. A number of inherited diseases have been shown to be caused by mutations or deletions in mitochondrial DNA.[47]

In terms of preimplantation genetic therapy, one possible scenario would be as follows: An unfertilized oocyte donated by an unaffected woman would be enucleated to remove all chromosomal genetic material and then parthenogenetically activated. It would then receive a nucleus from the embryo of an affected woman fertilized by her partner. The manipulated embryo would then have the nuclear DNA of the woman and her partner, but the normal mitochondrial DNA from the donor. It could be argued that a few defective mitochondria would be transferred along with the nucleus, since the transfer involves cell fusion. However, the number of mitochondria likely to be transferred is very small relative to the huge number present in the egg.

Scientific Possibilities Proscribed for Federal Funding

A number of other scientific issues were briefly considered by the Panel during their deliberations. Although the Panel concludes that these areas of research should be proscribed for Federal funding, they are described here for completeness. The reasons for prohibiting such research are further discussed in subsequent chapters.

Cross-Species Fertilization

There are exceptions to the Panel's prohibition of cross-species fertilization (see also chapter 6). Fertilization of hamster eggs with human sperm is widely used in infertility clinics as a test

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[46] C.L. Keefer, S.L. Stice, and D.L. Mathews, "Bovine inner cell mass cells as donor nuclei in the production of nuclear transfer embryos and calves," *Biology of Reproduction* 50:935–939, 1994; R.S. Prather, F.L. Barnes, M.M. Sims, J.M. Robl, W.H. Eyestone, and N.L. First, "Nuclear transplantation in the bovine embryo: Assessment of donor nuclei and recipient oocyte," *Biology of Reproduction* 37:859–866, 1987; S.M. Willadsen, "Nuclear transplantation in sheep embryos," *Nature* 320:63–65, 1986; S.M. Willadsen, "Cloning of sheep and cow embryos," *Genome* 31:956–962, 1989; S.L. Stice, and C.L. Keefer, "Multiple generational bovine embryo cloning," *Biology of Reproduction* 48:715–719, 1993.

[47] J.M. Shoffner and D.C. Wallace, "Mitochondrial genetics: Principles and practice," *American Journal of Human Genetics* 51:1179–1186, 1992; S.W. Ballinger, J.M. Shoffner, E.V. Hedaya, I. Trounce, M.A. Polak, D.A. Koontz, D.C. Wallace, "Maternally transmitted diabetes and deafness associated with a 10.4 kb mitochondrial DNA deletion," *Nature Genetics* 1:11–15, 1992.

for the fertilization competence of sperm.[48] These eggs are used to test the competence of a particular patient's sperm to penetrate an egg. However, the fertilized eggs are not permitted to develop nor is it likely that they would do so because of the wide evolutionary distance between the two species. Thus, the process has a clearly defined end point.

Similar cross-species uses of human gametes in therapeutic and diagnostic contexts would also be permissible, as long as development does not proceed beyond the one-cell stage. However, because of the close evolutionary relationship between humans and some primates, for example, chimpanzees, it is theoretically possible that human eggs fertilized with chimpanzee sperm might develop, at least to 14 days. Such cross-species fertilization would be unacceptable.

Formation of Chimeras

Studies with laboratory animals have shown that it is possible to mix together blastomeres from two (or more) different embryos, allow them to aggregate and develop into a blastocyst, and then be transferred to the uterus. The resulting animal is known as a chimera; all the tissues, including the germ cells in the ovary or testis, are derived from both sets of embryonic cells. Chimeras can also be obtained by injecting ICM cells or embryonic stem cells into a blastocyst and then transfer them to the uterus.

Studies of mouse chimeras made by either of these two methods (morula aggregation or blastocyst injection) have shown that extensive mixing takes place between the two cell lineages. This means that all the tissues of the resulting chimeric adult, including the brain and gonads, are a mosaic or patchwork of cells descended from both original embryos. As long as chimeras are made at the preimplantation stage, there is currently no way of directing the cells of one embryo into a particular tissue of the adult. This situation is unlike that which might occur if differentiated cells from an embryo or adult are injected or introduced into a late-stage fetus—a time when they could be directed to specific tissues, for example, the blood system.

Most studies with preimplantation embryos have involved making chimeras between different strains of mice, and they have produced much valuable scientific information, for example, about cell lineages and molecular and physiological processes.[49] A few chimeras between sheep and goats have been obtained. It is theoretically possible to make chimeras between human embryos and closely related primates such as chimpanzees, but, as discussed above, the fetus would have cells derived from both species in all tissues. In other words, it might be possible for the chimeric fetus to have large parts of the brain and/or gonads derived mostly from primate cells and other parts of the body derived mostly from human cells, a situation that would be totally unacceptable from both a medical and ethical standpoint.

Cases have been reported in the medical literature of people who are natural human-human chimeras, probably as a result of fertilization of both the egg and an abnormally large polar body by

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[48] J. Aitken, "On the future of the hamster oocyte penetration assay," *Fertility and Sterility* 62:17-19, 1994.

[49] A. McLaren, *Mammalian Chimaeras* (Cambridge: Cambridge University Press, 1976).

two different sperm or of spontaneous aggregation between two cleavage stage embryos.[50] These people often present clinically as hermaphrodites if they have a mixture of XX and XY cells, but otherwise appear to be normal. It could be argued that in the future the production of same sex human-human chimeras at the preimplantation stage might provide a route for gene therapy. However, the far-reaching implications of research into such an application, though beyond the scope of this Panel, needs extensive ethical and scientific analysis and public debate. It should be stressed, however, that if chimeras are made between human embryos of two different genotypes—even siblings of the same sex from one set of parents—then the brain of any resulting baby would still be a mixture of cells descended from both embryos. In the absence of extensive animal studies with chimeras in areas such as behavior and neuropharmacology, it is not possible to assess the overall risks involved in generating human-human chimeras of different genotypes at the preimplantation stage. For these and reasons discussed above and later in this report, the Panel found research involving the development of both human-human and human-nonhuman chimeras to be unacceptable for Federal funding.

Interspecies Uterine Transfer

Attempts to transfer blastocyst stage embryos into different species (e.g., rat and mouse) have failed because of immune rejection of the embryo by the host. This is likely to be a profound barrier to all interspecies embryo transfers. For these and ethical reasons discussed in chapter 6, the Panel found this research unacceptable for Federal funding.

Conclusions

In considering whether to recommend NIH funding for studies on ex utero preimplantation embryos, the Panel believed it critical to obtain information about the nature of the investigations that might be carried out, the clinical need for such work and its scientific and ethical justification, and the benefits, as well as problems, that might flow from it. The potential benefits were examined for their application in the short term to the relief of human suffering because of infertility and severe congenital defects and inherited diseases. However, it was also recognized that studies of preimplantation embryos could make important contributions over the long term to a variety of other medical problems.

In deliberating the scientific issues outlined in this chapter, members of the Panel repeatedly reminded themselves that NIH-funded research on preimplantation embryos would not only be subject to the special guidelines and, if approved, the special ad hoc national level review outlined in this report but also to the extremely stringent scientific peer review process applied to all other types of basic and clinical research. Among other things, peer review takes into account the scientific quality of the research, the qualifications of the investigators, their track record in research and ability to perform the experiments proposed, the appropriateness of the protocols to be used, and the importance and originality of the information to be gained.

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[50] A. McLaren, *Mammalian Chimaeras* (Cambridge: Cambridge University Press, 1976).

Several conclusions can be drawn from this review of the research. First, proposals for human studies that can only, by their very nature, be conducted on preimplantation embryos should be preceded by extensive experiments with nonhuman embryos, preferably those of more than one species. Second, there will always be some element of doubt as to whether preimplantation human embryos will behave in the same way as those of other animal species. This means that new techniques developed with nonhuman embryos should not be applied directly to human embryos that are to be transferred with the aim of establishing a pregnancy. Before transfer is considered, intermediate studies should be conducted on human embryos that are not intended for transfer. It is important to acknowledge that this scientific rationale was adopted by Steptoe and Edwards in their initial development of the clinical protocols used today in all IVF programs throughout the world.[51]

[51] P.R. Braude, V.N. Bolton, and M.H. Johnson, "The use of human pre-embryos for infertility research," in G. Bock and M. O'Connor (eds.), *Human Embryo Research: Yes or No?* (London: Tavistock Publications, 1986), pp. 63–82.

Chapter 3. Ethical Considerations in Preimplantation Embryo Research

Introduction

Current Federal regulations, based on the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, set forth the requirements for Federal funding of research involving postimplantation embryos and fetuses.[1] These regulations apply to "the product of conception from the time of implantation," and, without making any determination of the moral status of the postimplantation embryo in utero, they apply to it the same protection given fetuses. Thus, postimplantation embryos and fetuses may not be the subject of any research that carries more than minimal risk, unless such research is intended to be directly therapeutic to the individual embryo or fetus. These regulations apply equally to fetuses intended to be aborted, as well as to fetuses who are expected to develop to full term.

The regulations do not, however, address the status of ex utero preimplantation embryos, where research was made possible only through the development of human in vitro fertilization (IVF) techniques in the 1970s. It is the status of these embryos and the ethical use of such embryos in research that was considered by the National Institutes of Health (NIH) Human Embryo Research Panel. Research with fetuses is outside the scope of the Panel. The Panel addressed research with the ex utero preimplantation human embryo, or preimplantation human embryo, which refers to a fertilized ovum in vitro that has never been transferred back to or implanted itself in a uterus. This includes a fertilized ovum that has been flushed from a woman before implantation in the uterus, a procedure that is used infrequently and poses special risks.

This chapter identifies the ethical considerations in determining public policy for ex utero human embryo research. It is not intended to represent a complete philosophical discussion of the issue of embryo status but rather to focus on those aspects of the debate that are relevant to the establishment of public policies in a pluralistic society.

Approaches to Analyzing the Moral Status of the Human Embryo

Two broad approaches have been taken in debates over the moral status of the human embryo. One approach begins by proposing some single criterion of moral personhood. Beings that meet this criterion are believed to merit full and equal moral respect; those that do not are either denied respect or accorded a lesser status. The second approach is pluralistic. It sees moral respect and personhood as deriving not from one or even two criteria but from a variety of different and

[1] 45 CFR 46 Subpart B.

interacting considerations. The Panel considered both approaches in its deliberations regarding the moral status of the preimplantation embryo and its use in research.

Single Criterion Views

A single criterion approach to analyzing the moral status of the human embryo can lead to widely different conclusions. One view holds that the embryo is a person, a being meriting full and equal moral respect, from the moment of conception or fertilization because at this moment a unique diploid genotype comes into being. For those who hold this view, humanness, in a moral sense, is the possession of a distinctive human genetic identity.

Others arrive at this same conclusion by emphasizing the significant increase in potential for development that accompanies the transition from gametes to embryo.[2] Those who hold these views do not always specify what they mean by fertilization or conception, i.e., whether it is to be understood as egg penetration by the sperm, fusion of the membranes of the sperm and egg, pronuclei formation, syngamy (when chromosomes from the male and female gametes join), or the activation of zygotic genes, which in the human embryo occurs around the four- to eight-cell stage.[3] But all are agreed that the moment of fertilization/conception, however defined, is the crucial beginning of personhood.

For all who believe that moral personhood begins at conception the embryo ought to have the same moral rights as any other human research subject. No experimentation on the human embryo is permissible that would not also be allowed on the fetus in utero or on a newborn child.[4]

Moral positions emphasizing genetic identity or developmental potential offer a definitive standpoint on the status of the embryo, but they create paradoxes in logic and run counter to many widely accepted practices, including use of the intrauterine device and other contraceptive methods that work by preventing implantation. The equation of genetic diploidy with personhood leads to a logical paradox because twinning and the aggregation of two or more morula-stage embryos (sometimes inaccurately called "recombination") can occur well after fertilization.[5] The emphasis on

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[2] The U.S. Catholic Conference of Bishops selects fertilization as the point at which a "new and unique human being" comes into existence in *Documentation on Abortion and the Right to Life* (U.S. Catholic Conference: Washington, DC, 1976), p. 39. A concise statement of both the genetic and potentiality aspects of this position is offered by J.T. Noonan, Jr., in his essay "An almost absolute value in history," in J.T. Noonan, Jr. (ed.), *The Morality of Abortion: Legal and Historical Perspectives* (Cambridge: Harvard University Press, 1970), pp. 51–59.

[3] P.R. Braude, V. Bolton, and S. Moore, "Human gene expression first occurs between the four- and eight-cell stages of preimplantation development," *Nature* 332:459–461, 1988.

[4] R. Doerflinger (Secretariat for Pro-Life Activities, National Conference of Catholic Bishops), public testimony before the NIH Human Embryo Research Panel, February 2, 1994.

[5] The complexities of attributing genetic uniqueness to the preimplantation embryo are explored by K. Dawson in her essay "Fertilization and moral status: A scientific perspective," in P. Singer and K. Dawson (eds.), *Embryo Experimentation: Ethical, Legal and Social Issues* (Cambridge: Cambridge University Press, 1990), pp. 43–52. The embryo's lack of developmental individuality before the end of the second week forms the basis of N.M. Ford's and R.A. McCormick's rejection of the fertilization criterion, see N.M. Ford, *When Did I Begin?* (Cambridge: Cambridge University Press, 1989), pp. 181–182, and R.A. McCormick, "Who or what is the pre-embryo?" *Kennedy Institute of Ethics Journal* 1:1–15, 1991.

potential for development raises, but does not answer, the question of just *how much* potential is needed for moral respect.[6] It also ignores the fact that even though developmental potential increases at conception, it remains relatively low at least until implantation. For example, it is estimated that approximately 60 percent of conceptuses are spontaneously aborted in the first days and weeks of pregnancy. As the British Royal College of Obstetricians and Gynaecologists observes, "it is morally unconvincing to claim absolute inviolability for an organism with which nature itself is so prodigal."[7]

Among other single-criterion approaches to personhood, several positions exist that come to a very different moral conclusion about the status of the preimplantation embryo. One position bases full moral personhood on sentience–the ability to feel or to experience pain.[8] A second view emphasizes the beginning of brain activity or brain function.[9] This view derives from the belief that the brain is the essential organ underlying our specifically human capacities. It is also an effort to render an account of the beginning of life that is consistent with the criterion of whole-brain death as the end of life. A third position takes as the marker for the beginning of personhood certain well-developed cognitive abilities such as consciousness, reasoning ability, or the possession of self-concept.[10]

While these views can lead to different conclusions as to when personhood begins, all support the conclusion that the preimplantation embryo does not merit the same degree of moral protection given to children or adult human beings. The absence of a nervous system until after gastrulation or neurulation makes it certain that the preimplantation embryo cannot experience pain, has no brain activity, and is not conscious or self-aware.

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[6] P. Singer and K. Dawson, "IVF technology and the argument from potential," and S. Buckle, "Arguing from potential," in P. Singer and K. Dawson (eds.), *Embryo Experimentation: Ethical, Legal and Social Issues* (Cambridge: Cambridge University Press, 1990), pp. 76–89, 90–108.

[7] British Royal College of Obstetricians and Gynaecologists (RCOG), report of the RCOG Ethics Committee on In Vitro Fertilization and Embryo Replacement or Transfer (London: RCOG, 1983).

[8] P. Singer and D. Wells argue that sentience is a significant criterion for moral protectability in their *Making Babies* (New York: Charles Scribner's Sons, 1985). See also P. Singer, *Animal Liberation* (New York: Avon Books, 1990), ch. 1.

[9] This criterion of personhood is defended by B. Brody, *Abortion and the Sanctity of Human Life* (Cambridge: MIT Press, 1975), p. 114; J.M. Goldenring, "The brain-life theory: Towards a consistent biological definition of humanness," *Journal of Medical Ethics* 11:200, 1985; and H.-M. Sass, "Brain life and brain death: A proposal for a normative agreement," *Journal of Medicine and Philosophy* 14: 45–59, 1989. See also R.M. Veatch, "Definitions of life and death: Should there be consistency?" in M.W. Shaw and A.E. Doudera (eds.), *Defining Human Life: Medical, Legal, and Ethical Implications* (Ann Arbor: AUPHA Press, 1983), pp. 99–113.

[10] M.A. Warren offers five complex cognitive qualities she believes are requisite for moral personhood. These are consciousness and the capacity to feel pain, reasoning, self-motivated activity, the capacity to communicate, and the presence of self-concepts. See M.A. Warren, "On the moral and legal status of abortion," *The Monist* 57(1):43–61, 1973. A variant of this view is the interest position defended by philosopher B. Steinbock. This view differs in that neither self-consciousness nor the ability to reason or use language is essential for the possession of interests and, hence, moral status. However, an absolute minimum condition for having interests is a conscious awareness of one's surroundings. See Steinbock's "Ethical Issues in Human Embryo Research," a paper prepared for the Human Embryo Research Panel, January 1994, that can be found in volume II of this report; see also B. Steinbock, *Life Before Birth: The Moral and Legal Status of Embryos and Fetuses* (New York: Oxford University Press, 1992), Ch. 1.; J. Robertson, *Children of Choice: Procreative Freedom and the New Reproductive Technologies* (Princeton: Princeton University Press, 1994).

But these views also face conceptual and practical difficulties. Insistence on sentience as the criterion of personhood, for example, might require extending equal moral respect to animals. Some who hold this position welcome this extension, but others see it as running counter to our practices of using animals as a source of food or in scientific research. Equating personhood with an earlier stage such as the commencement of brain activity raises the same parallel with animal rights and a further question of what is meant by brain activity in this context. There are a variety of stages of early neural development to choose from, ranging from 6.5 weeks (time of earliest brain waves) to 24 to 28 weeks (when almost all sequences of nervous system development have begun).[11] Finally, a view based on consciousness, reasoning, or the possession of self-concept might lead to the exclusion of newborns from the class of protected subjects.[12]

A Pluralistic Approach

A second broad approach to understanding how personhood and moral protectability are established is pluralistic. It does not focus on a single criterion of personhood (such as genetic diploidy or self-concept) but emphasizes a variety of distinct, intersecting, and mutually supporting considerations. According to this view, the commencement of protectability is not an all-or-nothing matter but results from a being's increasing possession of qualities that make respecting it (and hence limiting others' liberty in relation to it) more compelling.[13]

Among the qualities considered under a pluralistic approach are those mentioned in single-criterion views: genetic uniqueness, potentiality for full development, sentience, brain activity, and degree of cognitive development. Other qualities often mentioned are human form, capacity for survival outside the mother's womb, and degree of relational presence (whether to the mother herself or to others).[14] Although none of these qualities is by itself sufficient to establish personhood,[15] their developing presence in an entity increases its moral status until, at some point, full and equal protectability is required.

According to this view, the increased potentiality for development that marks the transition from gametes to zygote—and the establishment at this stage of at least the beginnings of biological uniqueness—counsel giving the preimplantation embryo a measure of respect that is not due the sperm or egg. However, the absence at this stage of almost all other qualities evoking respect makes it

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[11] D.G. Jones, "Brain birth and personal identity," *Journal of Medical Ethics* 15:173–185, 1989.

[12] M. Tooley, *Abortion and Infanticide* (Oxford: Oxford University Press, 1983).

[13] This approach, linking the status of the fetus to stages of biological development, is discussed by B.M. Knoppers and S. LeBris, "Recent advances in medically assisted conception: Legal, ethical and social issues," *American Journal of Law & Medicine* 17(4):335, 1991. For a philosophical statement of this position, see R.M. Green, "Toward a Copernican revolution in our thinking about life's beginning and life's end," *Soundings* 66(2):152–173, Summer 1983.

[14] M.R. Maguire stresses the importance of maternal bonding to the fetus in establishing its moral sanctity in "Personhood, covenant, and abortion," in P.B. Jung and T.A. Shannon (eds.), *Abortion & Catholicism: The American Debate* (New York: Crossroad Publishing, 1988), pp. 100–120.

[15] Just as the absence or loss of any or one of these qualities might not be sufficient to justify withdrawing protectability from one already judged to be a person.

unreasonable to think of personhood as beginning here and places limits on the degree of respect accorded. These considerations appear to underlie the views of the status of the embryo advanced by groups like the U.S. Ethics Advisory Board in 1979, the Warnock Committee in Great Britain in 1984, and the Canadian Royal Commission on New Reproductive Technologies in 1993. The Ethics Advisory Board, for example, argued that "the human embryo is entitled to profound respect; but this respect does not necessarily encompass the full legal and moral rights attributed to persons."[16] And the Warnock Committee stated that although the human embryo is entitled to "some added measure of respect" beyond that accorded animal subjects, this respect "cannot be absolute, and may be weighed against the benefits arising from research."[17]

Formation of the primitive streak at 14 days of development and the beginning of cellular differentiation and organization of a single body axis marks yet another stage of development that merits an enhanced degree of protectability. As gestation continues, the further development of human form, the onset of a heartbeat, the development of the nervous system leading to brain activity and with this at least some of the physical basis for future sentience, relational presence to the mother, and capacity for independent existence all counsel toward according an increasing degree of protectability.[18] This line of thinking culminates at birth, where substantial development and independent existence outside the mother's womb provide the moral basis for full and equal personhood.

Implications for Public Policy

Americans hold widely different views on the question of the moral value of prenatal life at its various stages. These views are often based on deeply held religious and ethical beliefs. It is not the role of those who help form public policy to decide which of these views is correct. Instead, public policy represents an effort to arrive at a reasonable accommodation to diverse interests. To the extent possible, it takes into account the diverse moral sensibilities that exist in the community. Even constitutional reasoning acknowledges the importance of diverse but deeply held views.[19] Public policy employs reasoning that is understandable in terms that are independent of a particular religious,

[16] "Research Involving In Vitro Fertilization and Embryo Transfer," report of the Department of Health, Education, and Welfare Ethics Advisory Board, May 4, 1979, p. 101.

[17] Her Majesty's Stationery Office, "Report of the Committee of Inquiry into Human Fertilization and Embryology," Warnock Committee Report (London: 1984), p. 62.

[18] In U.S. law, an emphasis on the State's increasing interest in fetal life during the course of a pregnancy and stress on the capacity for independent existence permits States to proscribe abortion at the beginning of the third trimester of pregnancy, except when it is necessary to preserve the life or health of the mother; see *Roe v. Wade* 1973, 410 U.S. 113, 93 S. Ct. 705.

[19] See R.A. Charo, "Life after Casey: The view from Rehnquist's Potemkin Village," *Journal of Law, Medicine, and Health Care* 21(1):59-66, 1993.

theological, or philosophical perspective, and it requires a weighing of arguments in the light of the best available information and scientific knowledge.[20]

From the perspective of public policy, the weight of arguments appears to support the permissibility of embryo research within a framework of stringent guidelines. Each of the single criterion views considered by the Panel poses unresolved conceptual and practical difficulties, but, in any case, only one of these positions attributes personhood and full moral protectability to the preimplantation embryo. The remaining positions accord it either limited or no moral status. The pluralistic approach, with its emphasis on a variety of intersecting and mutually reinforcing criteria, is less subject to the specific criticisms aimed at each of the single criterion views. This approach also corresponds with the steady increase in moral respect many people give to prenatal life in its various stages from conception to birth. In contrast to many of the single criterion positions, the pluralistic approach accords some moral weight to the preimplantation embryo but it does not rule out well-justified research. The absence of developmental individuation, the lack of even the possibility of sentience and most other qualities considered relevant to personhood, the very high natural mortality at this stage, and the important human benefits research might achieve all support the conclusion that embryo research may be conducted under strict guidelines. In terms of public policy, this conclusion appears to be the most compelling one available.

This conclusion regarding the permissibility of research involving the preimplantation embryo is based on an assessment of its moral status and not solely on its location ex utero. It is true that once an embryo is transferred to a uterus and has implanted, current Federal regulations concerning fetuses apply. One implication of the Panel's conclusion that research on the ex utero human embryo is permissible is that such research may sometimes occur at a slightly later stage than would be permitted with an embryo that has implanted in the uterus. However, the treatment of an embryo in utero raises additional moral considerations, including those related to the well-being of the pregnant woman and any live-born child who may result—considerations that are not relevant where the ex utero embryo is concerned if there is no intention to transfer it to the uterus.

Distinctions Between Embryos Intended for and Not Intended for Transfer

It is important to recognize that when transfer to a uterus is intended, the preimplantation embryo is a research subject whose treatment raises distinct ethical issues. These issues are raised because research on the preimplantation embryo could result in harm to the child who will be born. Both in law and ethics, it is clear that fetuses who are brought to term are considered persons with full moral status and protectability.[21] It would therefore be unacceptable to transfer an embryo or

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[20] K.G. Gervais, "Moral majoritarianism vs. toleration as the basis of public policy," Third Annual Symposium on Law, Religion, and Ethics, Hamline University Law School, October 1990; J. Rawls, "The idea of public reason," in *Political Liberalism* (New York: Columbia University Press, 1993), pp. 212-254.

[21] The Warnock Committee Report (p. 63) observes that "under civil law in England and Wales the Congenital Disabilities (Civil Liability) Act 1976 allows, in limited circumstances, damages to be recovered where an embryo or foetus has been injured in utero through the negligence of some third person." In the United States, courts have generally ruled that a child who is born alive may recover damages by tort action for prenatal injury negligently inflicted at any one of several stages before birth: at preconception (through mutation of gametes), preimplantation (through mismanagement of the

embryos if it is reasonable to believe that children who could be born from these procedures will suffer harm as a result of the research. Even when research involves a diagnostic procedure, an embryo or embryos may not be transferred unless there is reasonable confidence that any child born as a result of the procedures has not been harmed by them. This distinction in treatment between embryos that will not be transferred and those that will is warranted by the need to avoid harms to the child who will be born.[22]

The distinction between embryos intended for transfer and those not intended for transfer involves considerations that are different from those arising in the context of fetal research. Federal law and regulations for the protection of human subjects in research require that research on fetuses that are to be aborted and those that are to be carried to term be given equal treatment.[23] The justification for not distinguishing between the two categories of fetuses rests partly on the consideration that a woman who is intending to have an abortion and has consented to potentially harmful research on the fetus she is carrying may change her mind and decide to proceed with the pregnancy.

It is not morally allowable to create a situation that compels a woman to undergo abortion or that, in the absence of abortion, risks serious harms both to the woman and to the child to be. However, this situation cannot arise where preimplantation embryos are involved, since even if a woman who donates an embryo for research changes her mind and wishes to try to establish a pregnancy, researchers, guided by a formalized consent process and with the support of an appropriate review committee, may justifiably refuse to transfer an embryo that carries a potential risk.

Fertilization of Oocytes for Research

The Panel considered whether it is ethically permissible to fertilize donated oocytes expressly for research purposes or whether researchers should be restricted to embryos remaining from infertility treatments that are donated by women or couples (see chapter 4). Panel members found this issue one of the most difficult to consider. In their deliberations, they noted that national-level bodies in several countries have previously approved the fertilization of oocytes for research purposes. The British Human Fertilisation and Embryology Authority approves and licenses research that involves the fertilization of oocytes if the goals and conduct of the research meet the Authority's standards.[24] The 1993 report of the Canadian Royal Commission on New Reproductive Technologies recommends allowing the fertilization of oocytes for research purposes under specified guidelines.[25] The State of Victoria, Australia, permits fertilization for research purposes up to the point

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in vitro embryo), at the previable stage (through teratogens in the workplace), and at the postviable stage (in the case of auto accidents). See R.F. Chase, "Liability for Prenatal Injuries," 40 A.L.R.3d 1222.

[22] T.H. Murray, "Moral obligation to the not-yet born: The fetus as patient," *Clinics in Perinatalogy* 14(2):329–343, 1987.

[23] 45 CFR 46.208; Section 498(a) and (b) Public Health Service Act.

[24] Human Fertilisation and Embryology Authority, *Code of Practice* (London: HFEA, 1993), pp. 40–41.

[25] *Proceed With Care*, report of the Royal Commission on New Reproductive Technologies (Ottawa: Minister of Government Services, 1993), pp. 638–641.

of syngamy (the joining of the male and female chromosomes about 24 hours after the beginning of fertilization).[26] As discussed in chapter 1, a previous American governmental body, the Ethics Advisory Board, concluded in 1979 that research involving the fertilization of donated oocytes was ethically acceptable in order to establish the safety and efficacy of in vitro fertilization.[27]

Those who are opposed to the fertilization and study of donated oocytes express several moral concerns. Invoking deeply held and widely shared beliefs about the significance of fertilization as the first step in bringing a potential human being into existence, those opposed to fertilization of oocytes for research argue that this step ought not be taken solely for research purposes, no matter how important these purposes might be. They maintain that development of embryos expressly for research is inherently disrespectful of human life, as well as being open to significant abuses. They also fear that this practice will lead to the instrumentalization of the preimplantation embryo and, by extension, of other human research subjects. They are particularly concerned that the development of embryos for research may result in the commodification of embryos and even their commercialization.

Many of those who hold this view believe that research on embryos remaining from infertility treatments (or preimplantation diagnosis) may be justified as a byproduct of the otherwise well-intentioned act of trying to conceive a healthy child, whereas the express fertilization of oocytes for research purposes lacks even this minimal justification.

Those who would permit the fertilization of oocytes expressly for research often argue that the resulting embryos have equivalent moral status to embryos remaining from infertility treatment, and thus they should be acceptable for research under similar guidelines.[28] These arguments are metaphysically complex and controverted, and the Panel did not come to any conclusion about their validity or weight.

However, those who would permit the fertilization of oocytes expressly for research also offer a number of arguments based on moral concerns such as the safety and health of women, children, and men. First, a ban on fertilizing donated oocytes for research would rule out much important research on oocyte maturation that may be of potentially great clinical benefit. In studying oocyte maturation, it is essential to find out whether the oocytes are fertilizable and whether they develop normally through cleavage stages. There is reason to believe that the low viability of some IVF embryos may be due to the rapid maturation of oocytes following hormonal stimulation. Studies of oocyte characteristics, followed by fertilization and studies of the developmental potential of embryos derived from different types of matured oocytes could lead to reducing the number of embryos returned to the woman. This would avoid the risks of multiple-gestation pregnancies and the resulting choice between a high-risk pregnancy and selective reduction of fetuses.

Research on oocyte maturation might also obviate the need for hyperstimulation in women undergoing in vitro fertilization or serving as egg donors. Hormonal treatment can be particularly

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[26] Infertility (Medical Procedures) Act (Victoria), 1987 Amendment to the Act.

[27] Ethics Advisory Board, "Summary and conclusions," *Federal Register* 44(18):35057, 1979.

[28] See, for example, N. Gerrand, "Creating embryos for research," *Journal of Applied Philosophy* 10:175–187, 1993.

risky for some infertile women suffering from polycystic ovarian disease syndrome, and, in some cases, in vitro oocyte maturation could be their only option for pregnancy.[29] Better understanding of oocyte maturation would allow women undergoing surgery to donate eggs to infertile couples. If fertility treatments are to improve and the risks to women and children are to be reduced, it is argued, more must be learned about oocyte maturation.

Second, a ban on the fertilization of oocytes for research purposes would preclude much research on the process of fertilization itself. Such a ban would hinder studies on the efficacy and safety of new contraceptives that work by interfering with the interaction of egg and sperm. Attempting fertilization is the only way to verify whether such contraceptives work.

Research on the freezing and thawing of unfertilized eggs would also be seriously impeded, since the only way to determine the safety and efficiency of this process is to fertilize the eggs and study their resulting chromosomes and rates of cleavage in vitro. The ability to freeze oocytes would greatly benefit women suffering from cancer or other diseases who wish eventually to have children but who must undergo chemotherapy or radiation treatments.

Third, a ban on the fertilization of oocytes for research purposes might preclude very important research on the effect on gametes and embryos of potentially harmful drugs or chemicals administered to women or to which women are exposed. One British study, for example, examined the effect on eggs of drugs used to induce ovulation.[30] Since possible risks to any children resulting from such pregnancies preclude transferring such embryos to a uterus and since some of this research must begin with unfertilized oocytes, this research could not go forward if the only permissible source of embryos was that of already fertilized embryos remaining from infertility treatments.

Fourth, a ban on the fertilization of oocytes for research purposes could impede particular kinds of research of great scientific and therapeutic value and for which an adequate number of embryos is essential to ensure validity. An example is research on genetic abnormalities or chromosomal imbalances arising or manifest during early embryogenesis and associated with birth defects and childhood or reproductive cancers.[31]

Fifth, in certain cases, permitting the fertilization of oocytes might be justified based on the limited number and suitability of embryos remaining from IVF treatments. Much valuable research that needs to be done and that is of great scientific or medical value may be slowed or halted if

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[29] A. Trounson, C. Wood, and A. Kansche, "In vitro maturation and the fertilization and developmental competence of oocytes recovered from untreated polycystic ovarian patients," *Fertility and Sterility* 62:353-362, 1994.

[30] A.A. Templeton, P. Van Look, R.E. Angell, R.J. Aitken, M.A. Lumsden and D.T. Baird, "Oocyte recovery and fertilization rates in women at various times after the administration of hCG," *Journal of Reproduction and Fertility* 76(2):771-778, 1986.

[31] A. Trounson, "Why do research on human pre-embryos?" in P. Singer and K. Dawson (eds.), *Embryo Experimentation: Ethical, Legal and Social Issues* (Cambridge: Cambridge University Press, 1990), pp. 14-25; J.C. Fletcher and P. Waldron, "Childhood Cancers and Human Embryo Research," a paper submitted to the Human Embryo Research Panel, April 1994. Some of the arguments in favor of research specifically into the mechanisms of genomic imprinting using human preimplantation embryos, which are presented in this paper, are open to debate and not accepted by all experts. Nevertheless, the need for studies on the origin of chromosomal abnormalities in embryos, some of which are associated with imprinting defects predisposing children to cancer, is widely accepted.

researchers are restricted to using only embryos remaining from infertility treatments or preimplantation diagnosis. Because the gametes and embryos derived from couples experiencing certain kinds of infertility tend to exhibit higher rates of abnormality, many of these embryos will be unsuitable for research designed to understand the normal processes of fertilization and embryo development. This problem is compounded by the fact that embryos remaining from infertility treatments are likely to be among the least viable of those produced. If the causes for the abnormalities in embryos from infertile couples are to be understood, in some cases limited numbers of embryos from fertile couples may be needed for comparison.

A final reason for permitting the fertilization and study of oocytes is that a complete prohibition in this area is likely to be very difficult—if not impossible—to enforce and is even likely to result in practices that exploit or harm women in infertility programs. In the words of the Australian Senate Select Committee, "any intelligent administrator of any IVF program can, by minor changes in his [sic] ordinary clinical ways of going about things, change the number of embryos that are fertilized."[32] The Canadian Commission adds that "[d]oing research on zygotes could put women enrolled in IVF programs under pressure to consent to donate unused eggs or zygotes. This pressure could be particularly acute if the development of zygotes for research purposes were prohibited."[33]

These arguments suggest that studies that require the fertilization of oocytes are needed to answer crucial questions in reproductive medicine. Reviewing all these considerations, the Panel concluded that it would not be wise to prohibit altogether the fertilization and study of oocytes for research purposes. The Panel had to balance important issues regarding the health and safety of women, children, and men against the moral respect due the preimplantation embryo. Earlier discussion of the moral status of preimplantation embryos, whatever the conditions under which they were fertilized, indicates that all preimplantation embryos have lesser moral status than existing persons. Given the conclusions the Panel reached about the lesser moral status of the preimplantation embryo, it concluded that the health and safety needs of women, children, and men must be given priority.

The Panel recognizes, however, that the preimplantation embryo merits respect as a developing form of human life and should be used in research only for the most serious and compelling reasons. There is also a possibility that if researchers have broad permission to develop embryos for research, more embryos might be created than is justified. In order to minimize this, the Panel believes that the use of oocytes fertilized expressly for research should be allowed only under the following two conditions:

- When the research by its very nature cannot otherwise be validly conducted. Examples of studies that might meet this condition include oocyte maturation or oocyte freezing followed by fertilization and examination for subsequent developmental viability and chromosomal normalcy and investigations into the process of fertilization itself (including the efficacy of new contraceptives).

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[32] Human Embryo Experimentation in Australia, quoted at p. 638, paragraph 3.31, in *Proceed With Care*, report of the Canadian Royal Commission on New Reproductive Technologies (Ottawa: 1993), vol. 1, p. 638.

[33] *Proceed With Care*, report of the Canadian Royal Commission on New Reproductive Technologies (Ottawa: 1993), vol. 1, p. 639.

- When the fertilization of oocytes is necessary for the validity of a study that is potentially of outstanding scientific and therapeutic value.

  An example of a study that might meet this condition is research to ensure that specific drugs used in reproductive medicine, such as those for inducing ovulation, have no harmful effect on oocytes and their developmental potential and do not compromise the future reproductive health of women.

  In another case, future discoveries might provide strong evidence that some forms of infertility, birth defects, or childhood cancer are due to chromosomal abnormalities, DNA modifications, or metabolic defects in embryos from the gametes of men and women of a particular category, for example, those exposed to specific environmental agents or carrying specific genetic traits. In order to test or validate such hypotheses a compelling case might be made for comparing embryos from at-risk couples with control embryos from "normal" couples. While embryos from many infertile couples in IVF programs might be suitable for this control group, in specific cases a compelling argument might be made that gametes donated by fertile individuals be carefully matched to those in the at-risk group for age and ethnic background are necessary for the most accurate and informative comparative scientific data.

The Panel wishes to make clear that oocytes should not be fertilized for research purposes because of a scarcity of embryos remaining from infertility procedures nor should they be fertilized just to have a ready supply of embryos at hand or for routine purposes such as toxicology studies.

The Panel also disapproves of financial inducements to either men or women to persuade them to relinquish their gametes. This disapproval was based not only on concern for the psychological impact on the donors but also on a reluctance to permit these precursors to conception and birth to become market commodities. (These issues are discussed more extensively in chapter 4.)

Time Limit for Human Embryo Research

The Panel discussed several stages in the development of the preimplantation embryo as possible times for a limit on human embryo research. Both ethical and scientific considerations were brought into the debate. The Panel devoted most of its attention to the biological events of gastrulation, the appearance of the primitive streak, and neurulation.[34]

Limits Set by Other Groups

The Panel reviewed policy documents regarding human embryo research in 11 countries other than the United States. One country prohibits all research with embryos, six allow very limited

[34] See chapter 2 for a discussion of these biological events.

research, and four "liberally permit research on embryos."[35] The latter four countries all require that research end by 14 days or by the time of the appearance of the primitive streak. Other countries' restrictions on research create a de facto limit at 3 to 5 days. A limit of 7 days has been proposed in two countries, but not yet enacted.[36]

The choice of 14 days or the appearance of the primitive streak (or any other discrete event) may appear somewhat arbitrary, since embryonic development is a gradual process. The consideration of this stage goes back at least as far as the 1970 paper "Fetal Development," by Andre Hellegers.[37] Hellegers cited the anomalies in embryonic development, particularly the ability of early embryos to twin and of two or more morula-stage embryos to aggregate (sometimes inaccurately called "recombination"), to question whether the preprimitive streak embryo has the status of an individual human being.

These questions were explored in much greater detail a few years later by James J. Diamond.[38] Diamond asserted that an individual human being cannot exist before 14 days' gestation—when the primitive streak appears. Some of the discussion material and papers prepared for the Ethics Advisory Board presented a similar view and persuaded members of that body to adopt a 14-day limit in their 1979 report.

Since that time, extensive discussion of the moral relevance of the primitive streak has appeared in both the scientific and the ethical literature.[39] The Ethics Committee of the American Fertility Society recommends that human embryos not be maintained for research beyond 14 days.[40] The Committee on Ethics of the American College of Obstetricians and Gynecologists argues that the lesser moral status of the preembryo (that is, the pre-primitive-streak embryo) permits research at that stage; their report does not address the ethical acceptability of research at later stages in the embryo's development.[41] The Canadian Royal Commission characterizes its choice of 14 days as a "morally

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[35] L.B. Andrews and N. Elster, "Cross-Cultural Analysis of Policies Regarding Embryo Research," a paper prepared for the NIH Human Embryo Research Panel, January 9, 1994. (See volume II of this report.)

[36] *Proceed with Care*, Report of the Canadian Royal Commission on New Reproductive Technologies (Ottawa: 1993), vol. 1, pp. 654–655.

[37] A. Hellegers, "Fetal development," *Theological Studies* 31:3–9, 1970.

[38] J.J. Diamond, "Abortion, animation, and biological hominization," *Theological Studies* 36:305–324, 1975.

[39] See, for example, C. Grobstein, *Science and the Unborn* (New York: Basic Books, 1988); N.M. Ford, *When Did I Begin?* (Cambridge: Cambridge University Press, 1989); and R.M. McCormick, "Who or what is the pre-embryo?" *Kennedy Institute of Ethics Journal* 1:1–15, 1991.

[40] American Fertility Society, Ethics Committee, "Ethical considerations of the new reproductive technologies," *Fertility and Sterility* 53(Suppl. 2):62S–63S, 1990.

[41] American College of Obstetricians and Gynecologists (ACOG), Committee on Ethics, "Pre-embryo Research: History, Scientific Background, and Ethical Considerations," ACOG Committee Opinion, Number 136 (Washington, DC: April 1994); testimony of R. Cefalo, Chair of the ACOG Committee on Ethics to the NIH Human Embryo Research Panel, May 4, 1994.

acceptable compromise in a pluralistic society in which there are various views about the relative importance of different stages of embryo development."[42]

The Significance of the Primitive Streak

The Panel reviewed biological information on the embryo both before and after the appearance of the primitive streak. In considering this information, the Panel debated the possible moral relevance of the appearance of the primitive streak in relation to embryo status. The following points were pertinent to the Panel's deliberations.

Before the appearance of the primitive streak, the embryo has the capacity of twinning, or becoming more than one distinct individual. Two or more cleavage-stage embryos or morulae can also aggregate ("recombine") and form a single chimera. Apart from the distinction between the cells of the trophoblast and the inner cell mass, the cells are totipotent and have not yet differentiated into specific kinds of tissues.

At the appearance of the primitive streak, the embryo proper is determined to be a distinct developing individual. Twinning of embryos and aggregation of two or more cleavage-stage embryos are no longer possible. With the appearance of the primitive streak, the cells of the inner cell mass begin to differentiate into various types of tissues. The embryonic disk (which develops from the inner cell mass) becomes a unified, organized, differentiating entity, the embryo proper, which develops continuously into the fetus and infant. The existence of a distinct individual is important to arguments for embryo status based on personal identity, continuity, or the theological concept of ensoulment (when the spiritual soul is joined to the developing organism). The absence of developmental individuation before the appearance of the primitive streak supports the claim that the embryo could not be a person before that time, while leaving open the question of personhood after formation of the primitive streak.

There is no neural tissue whatsoever before the appearance of the primitive streak; hence, there is no possibility of any kind of sentience. Soon after the primitive streak appears, the process of neurulation, or the development of the nervous system begins. The development of the nervous system, or neurulation, includes the development of the brain and the specific structures that underlie sentience and the ability to experience pleasure and pain.

Some panelists suggested that similar arguments of moral significance could be made for other important biological markers. The onset of a heartbeat at day 22, for example, marks the first time the embryo can be perceived (through ultrasound) by the outside world. Thus, it marks a moment when the relational element increases. Also, despite experience with brain death, it is the beating heart that is most strongly perceived to be the difference between life and death.

Other panelists wondered whether it might be permissible to extend research briefly beyond the primitive streak stage, since sentience is not possible until considerably later. Also, given the

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[42] *Proceed With Care*, report of the Canadian Royal Commission on New Reproductive Technologies (Ottawa: 1993), vol. 1, p. 635.

significance many persons attach to recognizable human form, its absence at this stage might also support more permissive guidelines.

The Panel agreed that, for public policy purposes, a clear time limit should be set. While the Panel finally agreed on the appearance of the primitive streak as the primary biological marker for a limit to research, it recognizes that the choice of this stage represents a compromise among competing viewpoints.

Use of the Primitive Streak as a Limit

The Panel carefully considered the advantages and disadvantages of using the appearance of the primitive streak as a limit beyond which research may not be conducted. The following information about the state of science played a role in the Panel's deliberations: It is not yet known whether the appearance of the primitive streak can be reliably observed, either morphologically or through molecular studies, when early human embryos are cultured in vitro. Furthermore, at the present time, the human embryo cannot be cultured in vitro from fertilization to the primitive streak and gastrulation stages with any reliability and efficiency. Two blastocysts have been recorded as surviving in culture to 8 days and 13 days, but it is unclear whether they were continuing to develop as they would have in vivo.[43]

The Panel noted that a 1982 report that describes successful culture of mouse embryos starting from the blastocyst stage through gastrulation and early organ formation and is still considered the "gold standard" for the state of mammalian embryo culture illustrates the inefficiency of the process (since only a very small percentage of mouse embryos developed beyond neurulation).[44] Evidence is still lacking that results can be obtained starting from fertilized eggs with a high degree of regularity or reproducibility and that methods can be transferred to other nonhuman animals.

The advantages of choosing the primitive streak as the definitive marker include the following:

- Its appearance indicates that the embryo proper is beginning differentiation and development as an organized individual. The moral significance of this stage, called developmental individuality, has been widely discussed and internationally accepted.

- Much important research could be conducted before the appearance of the primitive streak on such topics as preimplantation genetic and chromosomal diagnosis; the early development and gene expression of fertilized eggs, leading, for example, to diagnostic tests for developmental potential and determinations of the fertilized egg's competence to implant; the relative importance for the success of IVF of intrinsic and extrinsic factors such as oocyte and embryo quality versus culture medium and external conditions; development of

[43] K. Dawson, "Segmentation and moral status: A scientific perspective," in P. Singer and K. Dawson (eds.), *Embryo Experimentation: Ethical, Legal and Social Issues* (Cambridge: Cambridge University Press, 1990), pp. 53–64.

[44] L.T. Chen and Y.C. Hsu, "Development of mouse embryos in vitro: Preimplantation to the limb bud stage," *Science* 218:66–68, 1982.

cDNA databases that could be maintained indefinitely; the development of new contraceptives; studies directed toward cancer treatments; and the in vitro maturation, fertilizability, and developmental potential of immature oocytes from a variety of sources.

- Work on embryonic stem cells, their differentiation and their therapeutic potential, could proceed using the pluripotential cells of the blastocyst before gastrulation, when the inner cell mass is first distinguishable from the trophoblast.

- In view of the wide range of public views that were expressed to the Panel, it is advisable to set a clear time limit that will address the concerns of those who fear a slippery slope and possible abuses, while permitting research that promises to be significant for medical and therapeutic progress.

The disadvantages of using the appearance of the primitive streak as a limit beyond which research cannot be conducted include the following:

- Studies concerning agents or nutritional deficiencies that are possibly teratogenic to the embryo could not be applied to the later gastrulation and neurulation stages, which are thought to be highly and particularly sensitive to toxic agents in vivo.

- Certain kinds of restricted or multipotent stem cells (already partially committed to certain fates, such as hematopoietic stem cells) could not be obtained, since they would be present only around gastrulation and early neurulation.

- A time limit that is established in relation to present technical capabilities and the current state of science may unduly restrict scientific advances in the years ahead.

- There is significant scientific research that could be performed at each stage of embryonic and scientific development. Thus, it might be better to limit each research project according to the goals of that project, allowing it to continue as far, and only as far, as is necessary for that type of research.[45]

After deliberation on the advantages and disadvantages of applying a 14-day limit to research and on the significance of various proposed biological markers, the Panel determined the following:

- Research involving human embryos should be limited to the shortest period consistent with the goals of each research proposal.

- No research should be permitted after the time of the usual appearance of the primitive streak in vivo (14 days). The one exception to this limitation is for research whose goal is to determine whether the appearance of the primitive streak can be reliably identified in vitro.

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[45] CIBA Foundation, *Human Embryo Research: Yes or No?* (London: Tavistock Publications, 1986); (see p. 195 for comments of R. Edwards during conference discussion).

- At such time as there is evidence that the primitive streak can be reliably identified in vitro, research may be permitted up to the actual appearance of the primitive streak, even if this takes longer than 14 days in vitro.

- Research with donated embryos resulting from IVF treatment or clinical research may be conducted to develop cell lines through the isolation and culture of pluripotential stem cells from the blastocyst. While work using cells and cell lines would proceed beyond 14 days, these studies would not involve any embryo that is continuing to develop as an organized, integrated whole.

Conclusions

After weighing both pluralistic and single-criterion approaches to understanding how personhood and moral protectability are established, the Panel concludes that the preimplantation embryo warrants serious moral consideration but not the same as that due infants or children. The very high natural mortality, the absence of developmental individuation, the lack of even the possibility of sentience and most other qualities considered relevant to personhood, and the important human benefits research might achieve together counsel for allowing embryo research to be conducted under stringent guidelines. Thus, some research on the preimplantation human embryo should proceed.

In determining what sorts of research might be ethically acceptable, the Panel had to balance important issues regarding the health and safety of women, children, and men against the moral respect due the preimplantation embryo. Given its agreement that the preimplantation embryo warrants serious moral consideration, but not that accorded existing persons, the Panel concludes that the health needs of women, children, and men must be given priority in decisions about Federal funding of research.

The Panel, however, makes a distinction between research that is permissible with embryos that will not be transferred to the uterus and research permitted with embryos that will be transferred. This distinction is warranted by the need to avoid harms to any children born as a result of the procedures. Such risks are not present when transfer of an embryo is not involved.

In deliberating the permissibility of fertilizing oocytes expressly for research, the Panel finds that studies involving the fertilization of oocytes are needed to answer crucial questions in reproductive medicine. Weighing the importance of this research for the well-being of women and children, the Panel concludes that it would not be wise to prohibit altogether the fertilization of oocytes for research purposes. The Panel recognizes, however, that 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 research by its very nature cannot otherwise be validly conducted. The second condition requires that a compelling case be made to fertilize oocytes where this is necessary for the validity of a study that is potentially of outstanding scientific and therapeutic value.

The Panel determined that formation of the primitive streak at around 14 days of development and the beginning of cell differentiation and individual organization marks another stage of development that merits an enhanced degree of protectability. Thus, the Panel recommends that no research involving embryos be permitted after 14 days, with the exception of research to determine whether the appearance of the primitive streak can be reliably identified, which may occur later than 14 days in vitro, and research involving the development of cell lines from donated spare embryos, which would not involve an embryo that is continuing to develop as an organized, integrated whole.

Chapter 4. Sources of Gametes and Embryos for Research

Introduction

Having concluded that Federal funding of certain areas of research involving the ex utero preimplantation embryo is acceptable within stringent guidelines, the Panel went on to address another set of ethical dilemmas raised by the issue of the acceptability of various sources of embryos for research. In considering the issues concerning acceptable sources of gametes and embryos for research, the Panel identified four concerns that require special vigilance: informed consent, limits on commercialization, equitable selection of donors for research, and appropriate balancing of risks and benefits among subgroups of the population. These concerns parallel those addressed by well-established ethical guidelines for all human research. The selection of sources of gametes and embryos for research must be consistent with these established guidelines and in addition must show respect for the special qualities of the human gamete and embryo.

Informed Consent

The use of human tissue in research generally requires the consent of the donor. Thus, informed consent must be obtained from couples who donate embryos for research and from individuals who donate sperm or oocytes used to develop such embryos. Informed consent requires that prospective donors appreciate the nature and purpose of the proposed research. Thus, investigators need to disclose to potential donors information that a reasonable individual would consider pertinent to the decision of whether to donate.

The Panel recognizes that people may be willing to donate their gametes or embryos for certain types of research but not others. For example, individuals or couples who define the embryo as a person might donate only if the embryo will be transferred to a uterus. Others might donate only if there will be no transfer, because they do not want to generate offspring with whom they have no later relationship. Still others might not donate gametes or embryos if the investigator has a financial stake in the research.

Whenever possible, the prospective donors should be informed about the specific research protocol to be undertaken. The Panel realizes that such specific consent may be impossible, thus excluding from research currently frozen sperm or embryos whose sources may not have indicated their willingness to donate for research and may not be available for consent at the time the research is contemplated. For example, it may not be possible to locate anonymous sperm donors to obtain consent. In the future, this problem can be solved through prior consent for research at the time of donation. The Panel recommends that prior consent for research be required for all protocols that are subsequently devised, where prior consent means that donors are informed about the general nature and purpose of the research and are asked whether they would consent to all research or would

exclude research that involved fertilization, transfer in utero, or commercialization of the results of the research.

In another example, the Panel considered the possibility that in in vitro fertilization (IVF) programs, a donor may give sperm or oocytes to an infertile woman or couple with the intention of treating infertility. Because of the special nature of oocytes and sperm as carriers of genetic material, the Panel determined that donors do not relinquish all interest in their genetic material after donation. They might object if their genetic material were used for embryo research, rather than for treatment of infertility. Thus, the Panel believes that gametes donated for the treatment of infertility should not be used for research on embryos without the consent of the gamete donor as well as the embryo donor(s). In addition, with regard to embryo donation, consent must be obtained from all those who have been identified as the likely rearing parents of any children brought to term from the embryos. If transfer is to occur, the woman to whom an embryo is to be transferred must understand all risks to herself and any resulting children.

Problems may occur in obtaining informed consent if investigators also fill some other role that gives them power over the prospective donor. In IVF programs, one physician may serve as both researcher and personal physician. Women or couples might feel pressured into participating in research, because they are afraid to say no to their physician. The National Institutes of Health (NIH) should ensure that decisions to donate gametes or embryos are not coerced. For example, informed consent may be obtained by another investigator who is not the primary clinician or by a consent monitor.[1] Role conflicts may also occur if the investigator holds a position of authority over the potential donor, as might be the case with laboratory technicians or students. The burden of demonstrating that the consent process was voluntary and free of coercion rests with the investigator.

Limits on Commercialization

Many people view the buying and selling of research embryos as devaluing human life by defining it as property and harming men and women by defining them as potential sources of research materials. Some also fear that financial inducements to participate in human embryo research will lead to the exploitation of disadvantaged women, offering them powerful incentives to assume the risks of oocyte retrieval in order to sell their oocytes for research. There may be greater pressure on economically disadvantaged women and women of color to sell oocytes for research than for infertility treatment, because there is less demand in IVF programs for these sources. Similar concerns about the commercialization of body parts have led to Federal prohibitions on the purchase and sale of human organs and human fetal tissue for transplantation through the National Organ Transplantation Act and the Public Health Service Act.

In the United States, clinical reproductive services, including sperm banks, IVF programs, and egg brokers, however, are already commercialized. A large market for sperm has been in place for many years, and a market for eggs for IVF programs is now flourishing. Advertisements in student newspapers and medical school bulletin boards suggest that prices for eggs are already set by

[1] Consent monitors are neutral third parties who are present when investigators disclose information about research projects to prospective volunteers for a study. They can help assure that prospective volunteers have sufficient information to make an informed decision about participating in the study and that there is no duress or coercion by the investigator.

supply and demand. While NIH cannot control these clinical for-profit services, it can be sensitive to public concerns by proscribing the buying and selling of gametes and embryos for research.

The Panel believes that the selection of sources of research gametes and embryos should not involve the profit motive. It therefore recommends that no payment be permitted for gametes or embryos used in research, other than reimbursement for reasonable actual expenses incurred in the donation process. This ban covers brokers as well as sources of embryos and gametes. The Panel recognizes, however, that many IVF facilities compensate sperm and ova sources and that a retroactive ban on monetary compensation would mean that for the near future federally funded investigators would be denied access to a potentially important source of already existing embryos. The Panel believes this would present an unreasonable impediment to research, and it therefore recommends that a limited exception to this restriction should be possible after careful, case-by-case scrutiny though an ad hoc review process (described in chapter 5) for protocols that involve gametes from anonymous sources who were paid. The Panel would allow these exceptions to apply only to payment for gametes—not embryos—and recommends that these exceptions be made only for embryos already in existence at the time at which this report is accepted by the Advisory Committee to the NIH Director, should such acceptance occur. No compensation should be allowed for sperm or ova obtained after that date.

The Panel carefully considered whether participants in federally funded clinical studies involving IVF and preimplantation diagnosis research should be able to receive reasonable compensation for their participation in research. The Panel is concerned about financial inducements leading to the exploitation of disadvantaged women and recommends that there be no compensation, apart from defraying actual expenses incurred by the donor, for oocyte retrieval in nontherapeutic studies. The Panel also recognizes, however, the importance of ensuring that the benefits of research are fairly distributed in society and that compensation is one way of enhancing access to clinical research.

The Panel concludes that reasonable compensation in clinical studies should be permissible to defray a subject's expenses over and above the costs of drugs and procedures required in standard treatment, provided that no compensation or financial inducements of any sort are offered in exchange for the donation of gametes or embryos and so long as the level of compensation is in accordance with Federal regulations governing human subjects research and that it is consistent with general compensation practices for other federally funded experimental protocols. Human subjects regulations require local institutional review boards (IRBs) to ensure that payment levels do not become a coercive or undue influence on a prospective subject's decision to participate. The Panel wishes to underscore the importance of ensuring that the level of compensation does not become an undue influence to participation and that under no circumstances should such compensation ever include, or be construed to include, payment for gametes or embryos. Therefore, when women or couples have been compensated for their participation in research, special care must be taken to ensure that it is clear that the compensation is not in any way related to the donation of their embryos.

Another concern about commercialization is that it may undermine respect for human life and dignity. The Panel recommends that investigators be required to disclose to potential donors any personal financial stake in the results of the research. Without disclosure of such commercial interests on the part of researchers, consent to donate will not be truly informed. Some prospective donors would find plans for commercialization a compelling reason not to donate. While there is already precedent at the institutional level for requiring investigators to disclose their financial interest in the research, such disclosure is particularly important in human embryo research.

Equitable Selection of Donors and Subjects for Research

The selection of donors of research gametes or embryos must be equitable. In the past, poor and uneducated women—who were often women of color—were subjects of research procedures that would be considered unacceptable in the general population. Because of this history and concerns about discrimination and exploitation, protocols whose donors disproportionately represent people from disadvantaged groups need special justification or additional review beyond that of the local IRB. Such protocols may be justified in some cases; for instance, if they investigate conditions that are particularly prevalent in the given research population. Similarly, protocols that use as donors women or couples who are from foreign countries or who do not speak English also require special justification and additional review beyond that of the local IRB.

Furthermore, considerations of equity should include appropriate inclusion of donors as well as appropriate exclusion of donors. For example, the Panel noted that infertile women and men who, as a class, stand to gain from the potential benefits of research are often willing to bear a fair share of the burdens of research. It is ethically appropriate that subject groups who benefit from research contribute to the progress of that research, but participation must be fully voluntary.

A majority of the Panel supports a statement that there should be a commitment in federally funded studies to nondiscrimination and open access. Most members disagree, for example, with the recommendation made in 1979 by the Ethics Advisory Board that access to federally funded IVF research studies should be limited to legally married couples. Yet, while agreeing in principle to a commitment to equal access, other members of the Panel question the relevance of including such a statement in this report.

Acceptable Sources of Material for Research

The Panel gave careful consideration to the two distinct means by which a preimplantation human embryo can become available for research. The first is when embryos already fertilized for infertility treatments are not used for that purpose and are donated by the progenitors (these embryos are sometimes referred to as "spare" embryos). The second occurs when an oocyte is fertilized expressly for the purposes of research. The Panel also considered the ethical acceptability of the various donor sources of oocytes for research involving transfer, research without transfer, and research involving parthenogenesis. Possible donor sources include women in IVF programs, healthy volunteers, women undergoing pelvic surgery, women and girls who have died, and aborted fetuses.

In analyzing the acceptability of sources of gametes and embryos for research, the Panel emphasizes that the risks of the research, including the risks of gamete procurement, must be in proportion to the anticipated benefits. Risks that occur at various stages of research and in the context of diverse protocols restrict the acceptable sources of research gametes and embryos. For example, the need to consider the well-being of the future child when embryos are transferred to the uterus mandates that particular attention be paid to the acceptability of gamete and embryo sources and specifically that the gamete donors approve of the research as well as the transfer.

Issues specific to the sources of gametes and embryos for research and relative to the type of research to be performed are described in this section.

Embryos Donated by Couples in IVF Programs

Embryos donated by couples in IVF programs who have decided not to transfer the embryos themselves are an acceptable source of embryos for basic research that does not involve transfer as well as for clinical studies that may involve transfer, provided that all other ethical and scientific guidelines are met. In particular, informed consent must be obtained from any donor of gametes as well as from the woman or couple donating the embryos. Researchers should discuss with potential donors whether the research involves transfer to a uterus and disclose any personal financial interest in the research. When couples have been compensated for their participation in research, special care must be taken to ensure that it is clear that the compensation is not in any way related to the donation of their embryos.

Oocytes Fertilized In Vitro Specifically for Research

The ethical acceptability of fertilizing oocytes expressly for research was one of the most difficult issues considered by the Panel. The Panel decided, for reasons discussed in chapter 3, that Federal funding of research involving the fertilization of oocytes expressly for research should be allowed only under the two conditions described previously and provided that all other safeguards are in place. Difficulty obtaining sufficient numbers of untransferred embryos is not in itself an adequate justification for producing embryos for research.

In any type of research, steps should be taken to reduce to acceptable levels the risks to donors of human tissue. In the case of human embryo research, the most serious risks are medical risks to women undergoing oocyte retrieval. Also of concern to the Panel are risks to autonomy and dignity, i.e., the control of one's body. Thus, the Panel decided it was necessary to limit the types of risk that oocyte donors could be asked to undergo for research purposes.

In considering policies to ensure ethical treatment of gamete donors, the Panel follows the Canadian Royal Commission on New Reproductive Technologies in proposing three guidelines for the conduct of research involving oocytes fertilized in vitro specifically for research:[2]

- Women donating eggs should be subject to no additional surgically invasive procedures for these purposes. Thus, women who are undergoing scheduled gynecological surgery or egg removal for treatment of infertility may donate eggs for research, but eggs may not be solicited from women who are not otherwise undergoing a therapeutic or diagnostic procedure.

- Explicit consent for the development and use in research of the resulting embryos should be elicited from individuals who donate gametes used to develop embryos. It is not enough for a woman to consent to the donation of eggs in connection with a surgical procedure.

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[2] *Proceed With Care*, report of the Royal Commission on New Reproductive Technologies (Ottawa: 1993), vol. 1, pp. 639-640, 643-644.

She must also separately consent to the fertilization of these eggs for research purposes. Any financial interests of the investigator in the results of the research must be disclosed. The same explicit consent should be required from a donor of sperm.

- There should be no payment for eggs or sperm to be used for fertilization.

The Panel incorporated the Canadian Royal Commission guidelines into its own recommendations as to which sources of oocytes for research purposes are ethically acceptable.

Oocytes From Women in Infertility Treatment

If a woman who is in infertility treatment has had more eggs removed than she wishes to use for her own treatment, the Panel concludes that she may donate them for research. She must understand that the eggs will be fertilized and must agree as to whether the resulting embryos may be transferred or not. She may not receive compensation for the oocytes. The Panel thought that it is right for women and couples undergoing infertility treatment to assume a fair share of the burden of advancing research in this area given that they, as a class, stand to benefit most from the clinical applications that may result. However, the Panel also recognizes that infertility can cause great physical and psychological pain and that women undergoing treatment may be more vulnerable as a result. In order that women in IVF programs are not made to feel compelled to donate, great care must be taken to ensure that there is no undue, or even subtle, pressure to donate. The voluntary nature of such donations is essential and under no circumstances should women who do not wish to donate their oocytes ever feel pressured to do so.

Oocytes From Women Undergoing Scheduled Pelvic Surgery

Women undergoing scheduled pelvic surgery or other therapeutic or diagnostic procedures are a permissible source of oocytes for research, provided that the other guidelines are met. This category includes women undergoing oophorectomy and women who agree to ovarian biopsy or oocyte retrieval in addition to their primary procedure. Particular attention must be given to the ethical guidelines of reducing risks to donors and obtaining informed consent. The risks to the donor must be minimized, such as any risks resulting from changes in standard surgical procedures and from the administration of hormonal stimulation. Reducing the dose of any hormonal stimulation below that used in standard clinical practice would generally be appropriate to reduce the risk of hyperstimulation. Researchers must explain any changes from standard surgical procedures and if hormonal stimulation is used, the risks of such drugs. In the future, research on oocyte maturation in vitro may eliminate the need for hormonal stimulation of the oocyte donor. (See chapter 2 for further discussion of research.)

During the consent process, the donor must be informed that the oocytes would be used in research, that they may be fertilized, and whether they would be transferred to a uterus. While consent forms for surgery may authorize use of any removed tissues for research or teaching, the Panel believes that such a blanket consent is not sufficient in the case of human embryo research.

Donation of oocytes for research purposes without intent to transfer raises special concerns regarding risks to women. Some of the methods used to procure eggs, especially hyperstimulation,

involve the use of powerful drugs and invasive procedures that could pose risks to the health of women. Women undergoing treatment for infertility consent to these risks in return for potential therapeutic benefits and are therefore an acceptable source of oocytes for basic research that does not involve transfer, as well as for clinical studies that may involve transfer.

Women who are not scheduled to undergo a surgical procedure are *not* a permissible source of oocytes for embryos developed for research at this time, even if they wish to volunteer to donate their oocytes. The Panel is concerned about the risks that current methods of oocyte retrieval pose to the health of donors. In order to obtain a number of fertilizable oocytes, hormonal stimulation and an invasive procedure are now required. Because alternative sources of oocytes are available, the Panel believes that such risks to the donor cannot be justified.

The Panel, however, is willing to allow such volunteers to donate oocytes if the intent is to transfer the resulting embryo for the purpose of establishing a pregnancy. This is because the risks to the donor undergoing oocyte retrieval may be justified by the potential direct benefit to the infertile couple who hope to become parents as a result of the procedure. Absent the goal of establishing a pregnancy for an infertile couple, however, the lack of direct therapeutic benefit to the donor and the dangers of commercial exploitation do not justify exposing women to such risks.

Oocytes From Women and Girls Who Have Died

Women who have died are a permissible source of oocytes for research without transfer, provided that the woman had not expressly objected to such use of her oocytes and provided that appropriate consent is obtained. If the woman had expressed no objection to such use of her oocytes, she must have either consented to donation before her death or, in the absence of explicit consent on her part, next of kin may give consent at the time of her death.

The Panel determined that the donor or next of kin must understand that the ovaries specifically will be harvested, that oocytes will be used in research and might be fertilized, but not transferred to a uterus. The Panel recommends that embryos developed from cadaveric oocytes not be used in protocols that involve transfer to the uterus. Concerns about the meaning of parenthood and the significance of parent-child relationships persuaded the Panel that such transfer would be unwise. Proxy consent from survivors would not be acceptable if the woman herself had objected to donation of oocytes. Oocytes from women who have died should not be used in protocols in which researchers have a financial stake in the research unless the donor had specifically indicated her willingness to participate under such circumstances.

The Panel also decided that procedures for informed consent for preimplantation embryo research should be stricter than those required for organ transplantation, so that concerns about human embryo research will not undermine public willingness to donate organs for transplantation. Therefore, blanket willingness to donate organs for transplantation, as through an attachment to a driver's license, should not be considered adequate evidence of willingness to donate oocytes for research. Instead, donor or proxy consent must be specific, i.e., the donor or proxy must be informed that the organ being donated is the ovary and that it might be used in research that could involve the fertilization—but not transfer—of any oocytes derived from it. While the provisions of proposed uniform law such as the Uniform Anatomical Gift Act permit hospitals or physicians to use donated tissues for transplantation, research, or teaching, the Panel believes it would be unwise to

carry out human embryo research using cadaveric ovaries unless the donor or the next-of-kin understood that the derived oocytes would be used in research, that they may be fertilized, and that they would not be transferred to a uterus.

Additional safeguards should be applied. Provisions similar to those of the Uniform Anatomical Gift Act or relevant State and Federal law (42 U.S.C.A. 274 e) should apply regarding the prohibition of purchasing or selling human body parts. Additional safeguards should be developed or applied to ensure that a researcher who will be carrying out the subsequent research plays no role in caring for the dying patient or determining the time of death.

If the parents or guardians give surrogate consent, girls who have died may be used as sources of oocytes for research. The parents or guardian must understand that the oocytes may be fertilized but not transferred. Currently, parents have the right to choose to donate their deceased child's organs for transplantation or research. The Panel believes that there is no reason to impose special limits on parental rights to donate their deceased child's remains for human embryo research.

Oocytes From Aborted Fetuses

Many citizens strongly object to research involving the fertilization of oocytes from aborted fetuses. The objections of some citizens are based on their belief that if the fetal oocytes were obtained as a result of abortion—which they regard as immoral—then research using fetal oocytes is complicity with wrongdoing. Others point out that the compelling reasons that fetal tissue is used in therapeutic transplantation research are absent in the case of human embryo research and that there is no possibility of obtaining a medical history of the fetus or of either of its progenitors. Still other opponents fear a slippery slope: that fetal oocytes would ultimately be used in IVF programs, resulting in heretofore unheard of situations in which a child's genetic mother was never born. While this particular scenario is beyond our current scientific capabilities because of the great difficulties involved in the long-term in vitro development of oocytes from fetal ovaries, fears that research using fetal oocytes constitutes unacceptable tampering with the natural order of generations should be respected.

The Panel noted that Federal funding of basic research involving human fetal tissue has been ongoing for decades, including the use of fetal oocytes in research that does not involve fertilization. As of January 1993, the use of human fetal tissue from induced abortions for therapeutic transplantation research, which is studying potential uses of tissue for problems such as Parkinson's disease, may also be funded by the Federal Government.

Because of strong concerns about the importance of parenthood and the orderly sequence of generations as well as the need for detailed medical histories, the Panel concludes that research involving the transfer of embryos created from oocytes obtained from aborted fetuses should be unacceptable for Federal funding. The Panel also believes that it would be unwise public policy at this time to support research involving the fertilization of fetal oocytes even if they are not intended for transfer to the uterus. Such research should not be supported until the ethical implications are more fully explored and addressed by a national advisory body.

Parthenogenesis

Parthenogenesis is the activation of eggs to begin cleavage and development without fertilization. It has been shown in research involving parthenogenesis in mammals that when such parthenotes are transferred to the uterus, few reach the stage of implantation. The few that do reach implantation develop to various stages of early cell differentiation but then lose capacity for further development and die. Parthenotes fail to develop further, because they lack essential genes contributed by the sperm. All evidence therefore suggests that human parthenotes intrinsically are not developmentally viable human embryos. Thus, they do *not* represent a form of asexual reproduction.

Research on parthenotes, or activated eggs, might provide information on the specific role of the egg mechanisms in activating and sustaining early development, without generating a human embryo. Parthenotes may have research utility nearly identical to that of the normal embryo up to the blastocyst stage. In addition, a certain type of ovarian tumor originates from eggs that develop as parthenotes while still in the ovary. Research on parthenotes may shed light on problems arising during oocyte development that promote this type of tumor formation.

The Panel considered the parthenogenetic activation of oocytes as a source of research material and was sensitive to the symbolic dimensions of parthenogenesis and the possible moral and religious objections to research on parthenotes. The Panel also heard arguments that parthenogenesis would be an ethically acceptable source of research material because a parthenote, while it consists of human cells, is not a human embryo. It does not have a unique genetic identity and is incapable of developing in utero. Therefore, the use of parthenogenetically activated eggs for research may be morally acceptable to many citizens and scientists who might object to fertilizing eggs for research.

The Panel concludes that parthenotes are an acceptable source of research material, with strict prohibitions on transfer to a uterus. The requirements of informed consent must be met, with specific consent from the donor that development would be activated without fertilization. Guidelines concerning sources of oocytes for fertilization for research purposes apply similarly to acceptable sources of oocytes for research involving parthenogenesis.

Sources of Oocytes for Research on Parthenogenesis

The Panel concludes that women undergoing IVF procedures are a permissible source of oocytes for research involving parthenogenetic activation. Women undergoing scheduled pelvic surgery or other therapeutic or diagnostic procedures are a permissible source of oocytes, provided that the other guidelines for human embryo research are met. In such cases, particular care must be taken to explain any changes from standard surgical procedures and, if hormonal stimulation is used, the risks of such drugs. For such volunteers, whenever possible, reducing the dose of any hormonal stimulation below that used in clinical practice and likely to result in hyperstimulation syndrome would be appropriate.

Women *not* undergoing scheduled pelvic surgery or other therapeutic or diagnostic procedures and for whom donation would therefore subject them to invasive surgical procedures are not a permissible source of oocytes.

Ovaries of aborted fetuses are not a permissible source of oocytes for parthenogenesis unless the research by its very nature can only be conducted on fetal oocytes. Although Panel members noted that, technically, oocytes used for parthenogenesis are not fertilized and therefore would be subject to regulations governing human fetal tissue research, the mandate to the Panel requested that the issue of parthenogenesis be considered. The Panel recognizes the deep ethical sensitivities involved in the use of fetal oocytes for the generation of parthenotes. Moreover, it was made aware of the limited scientific utility of this source because of the great technical difficulties involved in long term in vitro development of oocytes needed to bring them to the stage required for parthenogenetic activation. The Panel therefore determined that only a compelling scientific need for fetal oocytes could ever justify their use in parthenogenesis and then only after stringent review.

Women who have died are a permissible source of oocytes for research involving parthenogenesis without transfer, unless the woman had expressly objected to such use of her oocytes and provided that appropriate consent is obtained. If the woman had expressed no objection to such use of her oocytes, she must have either consented to donation before her death or, in the absence of explicit consent on her part, next of kin may give consent at the time of her death. All relevant provisions of the Uniform Anatomical Gift Act must be met, as must regulations regarding autopsies and other guidelines for human embryo research.

While concluding that the parthenogenetic activation of oocytes for research is ethically acceptable, the Panel recognizes the importance of communicating to the public that such activated eggs, or parthenotes, lack the capacity to develop in utero. The Panel hopes that a prohibition on attempts at implantation of parthenogenetically activated eggs will help allay public concerns in this regard.

Oocyte Maturation Studies

Recognizing the strong objections held by some persons to many potential sources of oocytes and embryos, the Panel urges that the least controversial sources of research materials be given preference. Because of ethical concerns, the Panel has deemed unacceptable several potential source of oocytes and embryos. For example, in the short term, many frozen embryos in IVF programs are not acceptable for research, because the consent of the gamete donors was not obtained for research or because donors were paid. The Panel recognizes that valuable research of great potential benefit may be delayed by these restrictions, but it believes that the promise of potential benefits of research must be weighed against the need to show the respect due the human embryo and the need for informed consent of donors. To minimize delays to important research caused by a shortage of research oocytes and embryos, NIH should support studies of oocyte maturation. Greater ability to mature oocytes in vitro may allow oocytes from surgical or cadaveric specimens to be a practical source of oocytes for human embryo research that does not involve transfer in utero.

Conclusions

Informed consent must be obtained from couples who donate embryos for research and from individuals who donate the sperm or oocytes used to create such embryos. Informed consent requires that prospective donors appreciate the nature and purpose of the proposed research. In addition, the

Panel believes that investigators must disclose to potential donors any personal financial stake in the results of the research.

The Panel believes that the selection of sources of research gametes and embryos should not involve the profit motive. It therefore recommends that no payment be permitted for gametes or embryos used in research. Reimbursement for reasonable actual expenses incurred in the donation process and reasonable compensation of participants in clinical studies could be allowed provided such payments are not coercive.

The selection of donors of research gametes or embryos must be equitable and must consider the risks and potential benefits to the donor.

In general, the Panel concludes that, provided all conditions regarding consent and limits on commercialization are met, embryos donated by couples in IVF programs are acceptable sources of embryos for basic research that does not involve transfer, as well as for clinical research that may involve transfer.

The Panel concludes that women having oocytes removed in the course of infertility treatment are an acceptable source of oocytes for research. Women undergoing scheduled pelvic surgery or other therapeutic or diagnostic procedures are a permissible source of oocytes for research, provided that the other guidelines are met. Women who are not scheduled to undergo a surgical procedure are *not* a permissible source of oocytes for developing only research embryos at this time, even if they wish to volunteer to donate. However, such women may volunteer to donate where transfer of the embryo is intended.

Women who have died are a permissible source of oocytes for research without transfer—unless the woman had expressly objected to such use of her oocytes and provided that appropriate consent is obtained. If the woman had expressed no objection to such use of her oocytes, she must have either consented to donation before her death or, in the absence of explicit consent on her part, next of kin must give consent at the time of her death.

The Panel concludes by a narrow margin that it would be unwise public policy at this time to permit attempts at fertilization of fetal oocytes not intended for transfer without additional review and ethical study (see chapter 6). Many members of the Panel believe such research belongs in the unacceptable category. Because of strong concerns about the importance of parenthood and the orderly sequence of generations, the Panel concludes that research involving the transfer of oocytes obtained from aborted fetuses, as from other cadaveric sources, should not be acceptable for Federal funding.

Guidelines concerning sources of oocytes for fertilization for research purposes apply similarly to acceptable sources of oocytes for research involving parthenogenesis.

Chapter 5. Principles and Guidelines for Preimplantation Embryo Research

Introduction

Throughout its deliberations, the Panel considered the wide range of views held by American citizens on the moral status of preimplantation embryos. In recommending public policy, the Panel was not called upon to decide which of these views is correct. Rather, its task was to propose guidelines for preimplantation human embryo research that would be acceptable public policy based on reasoning that takes account of generally held public views regarding the beginning and development of human life. The Panel is aware that some citizens object to any research involving preimplantation embryos, and it considered carefully the thinking underlying their objections.

The Panel believes that certain areas of research are permissible based on the three primary considerations listed below. Different members of the Panel may have accorded different weight to each of these considerations in reaching a conclusion about the permissibility of such research.

- The promise of human benefit from research is significant, carrying great potential benefit to infertile couples, families with genetic conditions, and individuals and families in need of effective therapies for a variety of diseases.

- Although the preimplantation human embryo warrants serious moral consideration as a developing form of human life, it does not have the same moral status as infants and children. This is because of the absence of developmental individuation in the preimplantation embryo, the lack of even the possibility of sentience and most other qualities considered relevant to the moral status of persons, and the very high rate of natural mortality at this stage.

- In the continued absence of Federal funding and regulation in this area, preimplantation human embryo research that has been and is being conducted without Federal funding and regulation would continue, without consistent ethical and scientific review. It is in the public interest that the availability of Federal funding and regulation should provide consistent ethical and scientific review for this area of research. The Panel believes that because the preimplantation embryo possesses qualities requiring moral respect, research involving the preimplantation ex utero human embryo must be carefully regulated and consistently monitored.

General Principles for Preimplantation Embryo Research

Any research conducted on the human embryo or on gametes intended for fertilization should adhere to the following general principles, as well as the more specific guidelines described later.

Based on consideration of the issues presented in previous sections of this report, the Panel developed general principles that apply to all research involving preimplantation embryos, regardless of whether the research is classified as acceptable or warranting additional review (see chapter 6). If the conditions set forth in the following general principles are not met, the research is automatically considered unacceptable:

- The research must be conducted by scientifically qualified individuals in an appropriate research setting.

- The research must consist of a valid research design and promise significant scientific or clinical benefit.[1]

- The research goals cannot be otherwise accomplished by using animals or unfertilized gametes. In addition, where applicable, adequate prior animal studies must have been conducted.

- The number of embryos required for the research must be kept to the minimum consistent with scientific criteria for validity.

- Donors of gametes or embryos must have given informed consent with regard to the nature and purpose of the specific research being undertaken, i.e., whether fertilization and transfer are to occur. Consent must be obtained from all donors. In addition, with regard to embryo donation, consent must be obtained from all those who have been identified as the likely rearing parents of any children brought to term from the embryos. If transfer is to occur, the woman to whom an embryo is to be transferred must understand all known or anticipated risks to herself and any resulting children.

  It is not sufficient for a woman to consent to the donation of eggs in connection with a surgical procedure. She must also separately consent to the fertilization of these eggs for research purposes.

  Explicit consent for the development and use of embryos expressly for research purposes must be elicited from individuals who donate gametes used to fertilize oocytes for research.

  The responsibility for obtaining and ensuring full and informed consent lies with the investigator and the institutional review board (IRB). If the physician and the researcher are one and the same, the IRB may require consent monitors to ensure that free and

[1] The value of research depends on the validity of study design. One of the ethical justifications for research involving human subjects is the social value of advancing scientific understanding and promoting human welfare by improving health care. When a scientist is seeking funding from the Federal Government, rigorous review of the science is conducted through the agency's peer review process. Traditionally, research involving human subjects also is subject to review by a local Institutional Review Board (IRB) that provides an additional level of oversight to determine that the research is not only valid but of value and to determine whether "[r]isks to subjects are reasonable in relation . . . to the importance of the knowledge that may reasonably be expected to result" (CFR 46.111(a)(2)). Thus, this recommendation regarding validity of design is consistent with existing regulations concerning research with human subjects.

informed consent is obtained. In addition, the IRB should require consent to include financial disclosure by the investigator.

- There must be no purchase or sale of gametes or embryos used in research. Reasonable compensation in clinical studies should be permissible to defray a subject's expenses, over and above the costs of drugs and procedures required for standard treatment, provided that no compensation or financial inducements of any sort are offered in exchange for the donation of gametes or embryos and so long as the level of compensation is in accordance with Federal regulations governing human subjects research and that it is consistent with general compensation practice for other federally funded experimental protocols.

- Research protocols and consent forms must be reviewed and approved by an appropriate IRB and, for the immediate future, through an ad hoc review process to be established by the National Institutes of Health (NIH).

- There must be equitable selection of donors of gametes and embryos and efforts must be made to ensure that benefits and risks are fairly distributed among subgroups of the population.

- Out of respect for the special character of the preimplantation human embryo, research involving preimplantation embryos should be limited to the shortest time period consistent with the goals of each research proposal, and, for the present, research involving human embryos should not be permitted beyond the time of the usual appearance of the primitive streak in vivo (14 days). An exception to this is made for research protocols with the goal of reliably identifying in the laboratory the appearance of the primitive streak.

In addition to these general guidelines, the Panel developed the following specific guidelines for research on preimplantation embryos intended for transfer and for those not intended for transfer, as well as guidelines for research involving parthenogenesis. In addition, pursuant to the charge to the Panel, recommendations were developed regarding research that warrants further review and research that should not be supported. These are described in chapter 6.

Research on the Preimplantation Embryo Intended for Transfer

When transfer to a uterus is intended, research on the preimplantation embryo can also result in harm to the child who will be born—a research subject whose treatment raises distinct ethical issues. Both in law and ethics, it is clear that children who are brought to term are persons enjoying full moral status and protectability. It would therefore be unacceptable to transfer an embryo or embryos if it is reasonable to believe that children who could be born from these procedures may suffer harm as a result of the research.

Research on embryos that are to be transferred must be designed to avoid imposing harm on any children born as a result of the procedure or on the pregnant woman. Where research on embryos that are to be transferred is concerned, the following guidelines apply:

- Research on the preimplantation human embryo intended for transfer is justified only if it will provide generalizable knowledge important to the health or well-being of the developing human embryo, fetus, or newborn.

- The research must be related to facilitating the establishment of normal pregnancy or to providing direct benefit to the embryo to be transferred. Such research might include studies of preimplantation genetic diagnosis for the purpose of preventing genetic disease.

- The research procedures must be designed to avoid any additional risk of harm beyond what is ordinarily present in the clinical setting for assisted reproduction.

- Requisite animal research and human studies with nontransferred embryos must already have been completed and must provide evidence for the safety of the procedure.

Sources of Gametes and Embryos Intended for Transfer

Donors of gametes who are patients undergoing in vitro fertilization (IVF) and volunteer donors of gametes who are not otherwise undergoing IVF are acceptable sources of embryos intended for transfer. The Panel is willing to allow volunteer donors of oocytes even when they are not otherwise scheduled to undergo a diagnostic or therapeutic procedure, if the intent is to transfer the resulting embryo for the purpose of establishing a pregnancy. This is because the risks to the donor undergoing oocyte retrieval may be justified by the potential direct benefit to the infertile couple who hope to become parents as a result of the procedure.

Donation of embryos by individuals in IVF programs who have decided not to transfer the embryos or have decided to give them to another couple for transfer is ethically acceptable, provided that all other ethical and scientific guidelines are met. The recipient woman or couple would need to consent as well.

Out of respect for widespread moral sentiments about parenthood, gametes obtained from cadaveric sources, including aborted fetuses, must not be fertilized for transfer purposes in research protocols.

Research on the Preimplantation Embryo Not Intended for Transfer

Prior to conducting research on preimplantation embryos not intended for transfer, all requisite animal studies must be conducted. Certain concerns that arise when an embryo is intended for transfer do not apply in this case, such as sensitivities regarding lineage and potential risks to the live-born child. Still other concerns are identical to those raised when the embryo is intended for transfer, such as consent issues. Concerns also arise that are unique to protocols involving embryos that are not intended for transfer, such as acceptable donor sources for the specific research and the fertilization of oocytes expressly for research purposes.

Women donating eggs should be subject to no additional surgically invasive procedures for these purposes. For example, women whose ovaries are being removed via scheduled procedures for medical reasons may donate eggs for research, but eggs may not be solicited for research from women who are not otherwise undergoing a therapeutic or diagnostic surgical procedure.

Sources of Research Embryos Not Intended for Transfer

As with research involving preimplantation embryos intended for transfer, couples in IVF programs are acceptable donors of embryos for research not intended to lead to transfer.

Donated oocytes may be fertilized expressly for research only under the following two conditions:

- When the research by its very nature cannot otherwise be validly conducted. Examples of studies that might meet this condition include oocyte maturation or oocyte freezing followed by fertilization and examination for subsequent developmental viability and chromosomal normalcy and investigations into the process of fertilization itself (including the efficacy of new contraceptives). If oocyte maturation techniques were improved, eggs could be obtained without reliance on stimulatory drugs, lessening some of the potential risks for both patients and egg donors.

- When the fertilization of oocytes is necessary for the validity of a study that is potentially of outstanding scientific and therapeutic value. Panel members believe that special attention is warranted for such research because of their concern that attempts might be made to create embryos for reasons that relate solely to the scarcity of embryos remaining from infertility programs and because of their interest in preventing the creation of embryos for any but the most compelling reasons. An example of studies that might meet this second condition is research to ensure that specific drugs used in reproductive medicine, such as those for inducing ovulation, have no harmful effect on oocytes and their developmental potential and that these drugs do not compromise the future reproductive health of women.

  In another case, future discoveries might provide strong evidence that some forms of infertility, birth defects, or childhood cancer are due to chromosomal abnormalities, DNA modifications, or metabolic defects in embryos from gametes of men and women of a particular category, for example, those exposed to specific environmental agents or carrying specific genetic traits. In order to test or validate such hypotheses, a compelling case might be made for comparing embryos from at-risk couples with control embryos from "normal" couples. While embryos from many infertile couples in IVF programs might be suitable for this control group, in specific cases a compelling argument might be made that gametes donated by fertile individuals carefully matched to those in the at-risk group for age and ethnic background are necessary for the most accurate and informative comparative scientific data.

The Panel wishes to make clear that oocytes may not be fertilized for research purposes merely because of a scarcity of embryos remaining from infertility procedures nor may they be

fertilized just to have a ready supply of embryos at hand or for routine purposes such as toxicology studies.

Sources of Oocytes for Fertilization for Research

The Panel concludes that women who are undergoing IVF procedures may donate oocytes that are not needed for their own treatment, provided that other guidelines for human embryo research are met.

Women undergoing scheduled pelvic surgery are a permissible source of oocytes for research, provided that the other guidelines recommended by the Panel for preimplantation human embryo research are met. In such cases, particular care must be taken to explain any changes from standard surgical procedures and if hormonal stimulation is used, the risks of such drugs. For such volunteers, whenever possible, reducing the dose of any hormonal stimulation below that likely to result in hyperstimulation syndrome would be appropriate.

Women not undergoing scheduled pelvic surgery or other therapeutic or diagnostic procedures and for whom donation would therefore subject them to invasive surgical procedures are *not* a permissible source of oocyte donation for research without the intent to transfer.

Women who have died are a permissible source of oocytes for research without transfer, unless the woman had expressly objected to such use of her oocytes, and provided that appropriate consent is obtained. If the woman had expressed no objection to such use of her oocytes, she must have either consented to donation before her death or, in the absence of explicit consent on her part, next of kin may give consent at the time of her death. All relevant provisions of the Uniform Anatomical Gift Act must be met, as must regulations regarding autopsies and other guidelines for human embryo research.

Parthenogenesis

The Panel gave careful consideration to research involving the parthenogenetic activation of eggs without implantation. Parthenogenesis is the activation of eggs to begin cleavage and development without fertilization. Research on parthenotes might provide information on the specific role of the egg mechanisms in activating and sustaining early development, without generating a human embryo. Parthenotes from nonfertilized, but activated eggs might have research utility nearly identical to the normal embryo up to the blastocyst stage.

It has been shown in research involving parthenogenesis in animals that when animal parthenotes are transferred to a uterus, few reach the stage of implantation. The few that do reach implantation develop to various stages of early cell differentiation but then lose capacity for further development and die. All evidence therefore suggests that human parthenotes are not developmentally viable human embryos. The Panel recommends that research proposals involving parthenogenesis be considered ethically acceptable on condition that they meet the requirements of the general principles outlined above and that under no circumstances is transfer of parthenogenetically activated oocytes permitted.

Sources of Oocytes for Research on Parthenogenesis

The Panel concludes that women undergoing IVF procedures are a permissible source of oocytes for research involving parthenogenetic activation. Women undergoing scheduled pelvic surgery are a permissible source of oocytes, provided that the other guidelines recommended by the Panel for preimplantation human embryo research are met. In such cases, particular care must be taken to explain any changes from standard surgical procedures and if hormonal stimulation is used, the risks of such drugs. For such volunteers, whenever possible, reducing the dose of any hormonal stimulation below that likely to result in hyperstimulation syndrome would be appropriate.

Women not undergoing scheduled pelvic surgery or other therapeutic or diagnostic procedures and for whom donation would therefore subject them to invasive surgical procedures are *not* a permissible source of oocytes.

Ovaries of aborted fetuses are not a permissible source of oocytes for parthenogenesis unless the research by its very nature can only be conducted on fetal oocytes. Although Panel members noted that, technically, oocytes used for parthenogenesis are not fertilized and therefore such research would be subject to regulations governing human fetal tissue research, the Panel's mandate included issues regarding parthenogenesis. The Panel recognizes the deep ethical sensitivities involved in the use of fetal oocytes for the generation of parthenotes. Moreover, it was made aware of the limited scientific utility of this source because of the great technical difficulties involved in the long-term in vitro development of oocytes to bring them to the stage required for parthenogenetic activation. The Panel therefore determined that only a compelling scientific need for fetal oocytes could ever justify their use in parthenogenesis and only after stringent review.

Women who have died are a permissible source of oocytes for research involving parthenogenesis without transfer unless the woman had expressly objected to such use of her oocytes and provided that appropriate consent is obtained. If the woman had expressed no objection to such use of her oocytes, she must have either consented to donation before her death or, in the absence of explicit consent on her part, next of kin may give consent at the time of her death. All relevant provisions of the Uniform Anatomical Gift Act must be met, as must regulations regarding autopsies and other guidelines for human embryo research.

Review and Oversight of Preimplantation Embryo Research

Until 1993, the Department of Health and Human Services (and its predecessor agency, the Department of Health, Education, and Welfare, or HEW) was to rely on an Ethics Advisory Board (EAB) to determine whether specific proposals for embryo research would be ethically acceptable for Federal funding. HEW involvement in setting guidelines for research involving in vitro fertilization and/or embryo transfer was minimal, as most of the regulatory focus of the 1970s was on fetal research, research with pregnant women, and research involving children. The EAB was created in response to recommendations by the National Commission for the Protection of Research Subjects of

Biomedical and Behavioral Research.[2] The EAB's greatest power, however, lay in a new regulation that required all IVF experiments to be reviewed by the EAB prior to funding to ensure that they met EAB guidelines.[3]

The EAB embarked on a lengthy effort to set forth prospective guidelines concerning minimum qualifications for IVF researchers, standardization of laboratory conditions, and circumstances under which a conceptus may be created or destroyed. Because the Secretary of Health and Human Services did not act on the EAB's recommendations and funding for the EAB was subsequently withdrawn, the EAB's guidelines were never tested in the research community and public opinion about their implementation was never gauged.

The Panel does not recommend that the EAB be reconstituted for the purpose of reviewing research protocols involving embryos and 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 a 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 further possibility for 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.

The Panel wishes to retain the strengths of the old EAB, i.e., its assurance of consistent application of guidelines, without creating a new regulatory body. Therefore, the Panel recommends that all research proposals involving preimplantation human embryo research that are submitted to NIH for funding or that are proposed for conduct in the NIH intramural research program be subject to an additional review at the national level by an ad hoc body created with the discretionary authority of the Director of NIH. The purpose of the recommended review is to ensure that such research is conducted in accordance with guidelines established by NIH. This review is in addition to existing procedures and should occur after the standard reviews and approvals by study section and council have been completed. The additional review process should continue for at least 3 years. How this review process differs from the EAB process is detailed below. If the Director elects to dissolve this ad hoc review process after 3 years, a more decentralized review with certain additional oversight provisions, as specified further below, should begin.

Assuring Consistent Review

In vitro fertilization research involving the ex utero preimplantation human embryo has never been funded by the Federal Government, and there is virtually no experience with reviewing what in many instances will be complex and controversial research. Because this research involves human embryos, the goals of research in this area will be subject to continual debate and may often be misunderstood. For example, terms such as "cloning" and "parthenogenesis" have elicited dismay and misperception in the public mind. The review process will have to concern itself with the

[2] See National Research Award Act of 1974, Public Law 93-348.

[3] 45 CFR 46.204(d) deleted from 45 CFR 46, June 1, 1994.

controversial issues surrounding methods to procure gametes and the selection of gamete donors and will have to exercise vigilance in monitoring issues involving commercialization and informed consent.

Currently, the initial step in the review process for any research involving human subjects is submission to the local IRB. But with the exception of informed consent, many concerns regarding embryo research are issues about which IRBs have no special expertise. Further, even with such issues as informed consent there are considerations that are unique to this area of research, which involve donors and the use of gamete tissue (by its nature different from other bodily tissues).

NIH study sections cannot fill in the gap, because they are usually limited to reviewing the technical quality of the study design. Further, their membership is not likely to include experts in ethical matters. The second level of review provided by a statutorily mandated national advisory council or board of the institute is more likely to consist of lay members and is charged with reviewing grants—when appropriate—on grounds other than scientific or technical merit, but such councils are unlikely to have the expertise required to conduct adequate review.

In addition to ensuring a complete review, the Panel urges a *consistent* review. The current review system is to a significant degree decentralized. With few exceptions, IRBs will review human embryo research protocols infrequently. This research area is also likely to involve multiple study sections, institutes, and councils. These factors will impede the accumulation of precedents and cumulative knowledge about human embryo research necessary to achieving consistent application of the guidelines. For these reasons, the Panel believes 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.

In making this recommendation, the Panel was aware that there are at least two factors that caution against creating such a review mechanism. First, it is important to avoid the experience with the EAB, which created a roadblock that was used to halt all human embryo research. The Panel therefore proposes that this group be ad hoc in nature and created using the discretionary authority of the NIH Director. As indicated earlier, the Panel recommends that the review process continue for at least 3 years. Termination of this review mechanism should be at the discretion of the NIH Director.

Second, the Panel was concerned that establishing this additional step for all protocols might unnecessarily delay the conduct of this research. The review that is recommended here is best situated at the conclusion of the existing review process. The Panel has carefully avoided specifying how such a group might operate but anticipates that with respect to certain types of protocols the ad hoc group might wish to institute some system for expedited review as well as criteria on which to exclude from eligibility for Federal funding certain types of research.

Obviously, some delay in the conduct of research because of the review recommended here is unavoidable, and the Panel has tried to minimize this potential problem. The Panel believes that the presence of an ad hoc group in the short term will ultimately expedite research. Research protocols that arguably could be placed in a "warranting further review" or "unacceptable" category can be carefully reviewed to ascertain whether such categorization is warranted. The Panel believes that, in the long term, human embryo research will benefit from careful attention to the details of its

initiation. Such review will also help retain public confidence that this research is being conducted in a manner that is broadly acceptable to society.

Once precedent and experience have been established through the ad hoc review body and it is dissolved, research involving preimplantation embryos and fertilization of ova that is presumed to be acceptable will be subject to all the ordinary and routine forms of review necessary for NIH-sponsored research. These include review by a local IRB, an NIH study section committee, and the council for each of the institutes.

When the ad hoc review body ceases to exist, the Panel recommends that all such research proposals continue to be specially monitored by the councils and the NIH Office for Protection from Research Risks (OPRR). This monitoring would include a commitment by the councils to pay particular attention to the protocols as they are presented for approval, in order to ensure that the local IRB and study committee have correctly applied the guidelines adopted by the Director of NIH. It would also entail having NIH periodically (e.g., twice yearly) publish a summary of funded protocols, along with commentary on any particularly difficult problems encountered in applying the guidelines. This summary should be published in the NIH *Guide to Grants and Contracts* and thereby made available to local IRBs throughout the country, as well as to the councils of the various institutes, in order to ensure consistency in their application of the guidelines. As embryo research has been totally unfunded for nearly two decades, NIH may wish to disseminate its view that particular types of research are presumably acceptable or unacceptable. For this purpose, the existing practice of sending out research alerts from OPRR could probably suffice. In addition, OPRR might sponsor several meetings at major research institutions around the country to disseminate the new guidelines and engender a continuing discussion with the public and the research community about their acceptability and workability.

Finally, the Panel urges the NIH Director to use the councils or specially created ad hoc panels to engage in special review for certain research proposals that require a particularly strong showing of scientific merit to justify their ethically or politically controversial nature.

Chapter 6. Categories of Preimplantation Embryo Research

Introduction

While it is clearly impossible to anticipate every type of research project that might be proposed, the Panel's charge required that it classify types of embryo research into three categories: acceptable for Federal funding, warranting additional review, and unacceptable for Federal funding. If all the conditions outlined in the general principles are met, then a research proposal is eligible for review by the proposed National Institutes of Health (NIH) ad hoc body, after having completed review by the local institutional review board (IRB) and the NIH study section. The following categories of research were developed based on the ethical and scientific criteria for research established by the Panel. The classifications are intended to provide guidance for future review bodies with the anticipation that categories will make eligible certain types of protocols for expedited review, as well as clearly delineate those considered ineligible for Federal funding.

Acceptable for Federal Funding

A research proposal is presumed acceptable if it is in accordance with the guidelines described in chapter 5 and is not described below as warranting additional review or being unacceptable. Thus, a protocol not in the last two categories would be classified acceptable if it is scientifically valid and meritorious; relies on prior adequate animal studies and, where appropriate, studies on human embryos without transfer; uses a minimal number of embryos; documents that informed consent will be obtained from acceptable donor sources; involves no purchase or sale of gametes or embryos; does not continue beyond the appearance of the primitive streak (which normally occurs at 14 days in vivo); and has passed the required review by a local IRB, appropriate NIH study section and council, and, for the immediate future, the additional review body at the national level established at the discretion of the NIH Director.

Proposals in this category must also meet the specific guidelines set forth in this report concerning types of research (i.e., transfer, no transfer, parthenogenesis) (see chapter 5) and acceptable sources of gametes and embryos (see chapter 4). Once precedent and experience have been established through the ad hoc review body and the review body is dissolved, research presumed to be acceptable will be subject to all the ordinary and routine forms of review necessary for NIH-sponsored research. These include review by a local IRB, an NIH study section committee, and the council for each of the institutes. Examples of such proposals the Panel finds to be acceptable for Federal funding include, but are not limited to, the following:

- **Studies aimed at improving the likelihood of a successful outcome for a pregnancy.**
- **Research on the process of fertilization.**

- **Studies on egg activation and the relative role of paternally derived and maternally derived genetic material in embryo development (parthenogenesis without transfer).**

- **Studies in oocyte maturation or freezing followed by fertilization to determine developmental and chromosomal normality.**

- **Research involving preimplantation genetic diagnosis with and without transfer.**

- **Research involving the development of embryonic stem cells but only with embryos resulting from IVF treatment for infertility or clinical research that have been donated with the consent of the progenitors.**

- **Nuclear transplantation into an enucleated, fertilized or unfertilized (but activated) egg without transfer with the aim of circumventing or correcting an inherited cytoplasmic defect.**

  With regard to the last example, the Panel thought carefully about the implications of approving research that involved manipulating nuclear material. The Panel distinguishes this research from nuclear transplantation for cloning purposes, that is for simply increasing the number of genetically identical embryos, research that they found clearly unacceptable. Because the intent of the research is to advance a technique that has a therapeutic aim (that is, helping women with cytoplasmic diseases to have children) and because the research would not involve the mixing of genetic material of two embryos, many Panel members feel that the ethical concerns can be balanced by the potential benefits. With these considerations in mind, a narrow majority of Panel members conclude that the research should be acceptable for Federal funding. However, the Panel wishes to acknowledge that nearly as many Panel members believe that the ethical implications of research involving the transplantation of a nucleus, whether transfer was contemplated or not, warrant further study before the research can be considered acceptable for Federal funding.

  As noted below, a clear majority of the Panel does not wish at this time to allow research involving the transfer to a uterus of an embryo that received a nuclear transplant. This is because a great deal of basic research must be completed before the technique could be considered for human studies and, even then, the ethical implications of establishing a pregnancy in this way must be carefully studied.

In addition to the above examples of acceptable research, the Panel singled out two types of acceptable research for special consideration. The Panel has placed these two types of research in the acceptable category, but for reasons explained below urges that all such studies receive very careful scrutiny during the recommended ad hoc review process. The two types of research are as follows:

- **Research involving the use of existing embryos where one of the progenitors was an anonymous gamete source who received monetary compensation. (This exception would apply only to embryos already existing at the time at which this report is accepted by the Advisory Committee to the Director, NIH, should such acceptance occur.)**

The Panel recognized that many IVF facilities compensate sperm and ova sources and that a retroactive ban on monetary compensation would mean that for the near future a potentially important source of embryos would be off limits. The Panel believes this would present an unreasonable impediment to research, and it therefore recommends that a limited exception to this restriction should be possible after careful, case-by-case scrutiny through an ad hoc review process (described in chapter 5) for protocols that involve gametes from anonymous sources who were paid. The Panel would allow these exceptions to apply only to payment for gametes—not embryos.

- **A request to fertilize ova where it is necessary for the validity of a study that is potentially of outstanding scientific and therapeutic value.**

  As stated in the general principles, scarcity alone is not a justification for the creation of embryos specifically for research purposes. It is anticipated, however, that the scientific, methodological, and statistical requirements of specific research protocols of outstanding scientific and therapeutic value may require the creation of a minimal number of control or experimental embryos (not intended for transfer) to ensure validity and statistical power. Future discoveries might provide strong evidence that some forms of infertility, birth defects, or childhood cancer are due to chromosomal abnormalities, DNA modifications, or metabolic defects in embryos from gametes of men and women of a particular category; for example, those exposed to specific environmental agents or carrying specific genetic traits. In order to test or validate such hypotheses a compelling case might be made for comparing embryos from at-risk couples with control embryos from "normal" couples. While embryos from many infertile couples in IVF programs might be suitable for this control group, in specific cases a compelling argument might be made that gametes donated by fertile individuals carefully matched to those in the at-risk group for age and ethnic background are necessary for the most accurate and informative comparative scientific data. Such research might be permitted after careful scrutiny of the proposal. Panel members believe that special attention is warranted for such research because of concern that attempts might be made to create embryos for reasons that relate solely to the scarcity of embryos remaining from infertility programs and because of the Panel's interest in preventing the creation of embryos for any but the most compelling reasons.

Research That Warrants Additional Review

The Panel places research areas in the category of warranting additional review because the proposals are of a particularly sensitive nature. The Panel did not make a determination as to the acceptability of these proposals, and recommends that there be a presumption against funding such research for the foreseeable future. This presumption could be overcome only by an extraordinary showing of scientific or therapeutic merit, together with explicit consideration of the ethical issues and social consequences. Such research proposals could be funded only after review by a broad-based ad hoc body created at the discretion of the Director, NIH, or by some other formal review process.

The areas of research that the Panel determines should be placed in the category of warranting additional review are as follows:

- **Cloning by blastomere separation or blastocyst splitting without transfer.**

  Blastomere separation might be a useful method for generating populations of genetically identical embryos for certain scientific studies not involving transfer. This would include methods designed to increase the viability and developmental potential of embryos in general and to develop diagnostic tests for viability. The ethical implications of such research, however, need careful study before Federal funding is considered. Research involving blastomere separation with transfer, it should be noted, was placed in the unacceptable category, for reasons discussed below.

- **Research between the appearance of the primitive streak and the beginning of closure of the neural tube.**

  As discussed in chapter 2, severe defects in the development of the nervous system, such as craniorachischisis and anencephaly, may result from failure of the process by which the neural plate folds up into a hollow tube forming the brain vesicles and spinal cord. This process occurs largely during days 17 to 21. Before closure the neural tissue is extremely primitive and no specialized neuronal connections are formed. In the future, research of exceptional merit might increase understanding of genetic, nutritional, and environmental factors associated with failure in neural plate closure and consequent developmental defects in the human embryo. Because such research requires the use of embryos beyond the common 14-day limit, additional review would be required prior to funding.

  While the philosophical and ethical literature contains extensive discussion of the moral permissibility of embryo research until the appearance of the primitive streak, to date there has been little discussion of the morality of extending research to a somewhat later stage. Before research in this category is considered for Federal funding, NIH should ensure a thorough consideration of the moral and ethical issues involved, as well as the potential consequences of moving beyond the internationally accepted boundary for embryo research.

- **Research that uses fetal oocytes for fertilization without transfer or for parthenogenesis.**

  Because fetal oocytes have certain characteristics that set them apart from oocytes obtained from older ovaries, it is possible that specific research might require their use for comparative purposes to better understand fertility and developmental problems associated with older, environmentally exposed oocytes. This consideration persuaded a bare majority of the Panel that research involving fetal oocytes might have potential scientific and medical benefits and that Federal funding of such research should be considered in the future after further study of the ethical concerns and public sensitivities. However, the Panel wishes to make clear that its decision to recommend that this research be in the further review category, rather than the unacceptable category, was made by a narrow margin.

- **Nuclear transplantation into an enucleated, fertilized or unfertilized (but activated) egg with transfer for the purpose of circumventing or correcting an inherited cytoplasmic defect.**

  This application of nuclear transplantation moves the nuclear material into a different cytoplasmic environment without increasing the final number of embryos. It could be used therapeutically to overcome disease that results from mutations in mitochondrial DNA. Since the mitochondria come from the egg, defects are maternally transmitted from generation to generation. All the eggs of an affected woman carry the defect, so that all her children are also affected and there is no possibility of selection of unaffected eggs by preimplantation genetic diagnosis. Nuclear transplantation could stop the cycle of maternal inheritance, and there would be no need to repeat the process of nuclear transplantation in the next generation.

  Notwithstanding the important potential therapeutic benefits that may result if this technique is developed, the Panel believes that the risks involved in this research and the ethical questions raised by it need to be studied and addressed before clinical studies could be considered.

- **Embryonic stem cell research that uses deliberately fertilized oocytes.**

  The therapeutic utility of embryonic stem cells lies in their potential as a source of differentiated cells for transplantation and tissue repair. If this potential is realized, a case might be made for obtaining cell lines from a range of different genotypes, in particular those encoding different transplantation antigens, so that the benefits could be reaped by people of different ethnic backgrounds, for example. In order for this to occur, the deliberate fertilization of oocytes might be necessary in addition to donated embryos from IVF programs.

  In this regard, the Panel was sensitive to the special ethical concerns raised by the creation of embryos for this purpose. While the Panel as a whole is convinced of the broad potential benefits, individual members are divided in their views about whether oocytes should ever be deliberately fertilized for this purpose. The Panel's decision to place this research in the further review category was made by a narrow majority of members. A number of other members felt that the research was acceptable for Federal funding without further ethical study, but some also believed that the research should be considered unacceptable for Federal funding. One member who found this research unacceptable argued that the development of embryos explicitly for research ought only to be permitted under the two conditions already agreed to by the Panel and believed that such research did not seem to satisfy either of these conditions (see appendix B).

  The Panel wishes to note that it is very likely that future research may make the deliberate fertilization of oocytes for this purpose unnecessary. For example, it may be possible to specifically alter the genes of the stem cell lines, controlling transplantation antigens. In addition, research with animals may show that it is possible to transfer nuclei from differentiated adult cells into enucleated eggs and obtain normal development to the blastocyst stage. In this case, it might be possible to obtain stem cell lines from the blastocyst that would have a genotype identical to that of the adult donor. In this case,

following adequate animal work, experiments involving transfer of human nuclei into enucleated eggs not destined for implantation could be the subject of review. It should be noted that if these experiments involved transplantation of nuclei from differentiated cells of adults into enucleated, activated or mature oocytes, no fertilization of male and female gametes would be involved.

Research Considered Unacceptable for Federal Funding

Four ethical considerations entered into the deliberations of the Panel as it determined what types of research were unacceptable for Federal funding: the potential adverse consequences of the research for children, women, and men; the respect due the preimplantation embryo; concern for public sensitivities on highly controversial research proposals; and concern for the meaning of humanness, parenthood, and the succession of generations.

Throughout its report, the Panel considered these concerns as well as the scientific promise and the clinical and therapeutic value of proposed research, particularly as it might contribute to the well-being of children, women, and men. Regarding the types of research considered unacceptable, the Panel determined that the scientific and therapeutic value was low or questionable, or that animal studies did not warrant progressing to human research.

Research proposals in the unacceptable category are not to be federally funded for the foreseeable future. Even if claims are made for their scientific or therapeutic value, the serious ethical concerns would need to be adequately addressed. Such research includes the following:

- **Cloning of human preimplantation embryos by separating blastomeres or dividing blastocysts (induced twinning), followed by transfer to the uterus.**

  This technique has been advocated for clinical use for a number of reasons, for example, for increasing the fertility of infertile couples from whom only a few fertilized eggs are recovered, for minimizing the need for subsequent egg retrievals should the first transfer fail (in combination with embryo freezing), and for increasing the efficiency of preimplantation genetic diagnosis. However, as discussed in chapter 2, extensive animal studies have shown that the inherent viability of embryos developing from separated blastomeres or blastocysts is reduced compared with that of unmanipulated, intact embryos. For these and other reasons, it can be argued on scientific grounds that only very modest gains, if any, might be expected in the foreseeable future from applying blastomere or blastocyst splitting techniques to the treatment of infertility, thereby unnecessarily raising the hopes of infertile couples. The scientific merits of using the techniques for improving the efficiency of preimplantation genetic diagnosis are also not compelling at this time.

  Because the Panel did not find scientific evidence that blastomere separation was therapeutically promising, it concluded that Federal funding of research involving blastomere separation with transfer to the uterus was inappropriate. Having reached this conclusion, the Panel did not debate in detail the ethical issues raised about various possible applications of such research. Such concerns include creating genetically identical individuals who could be born at different times, storing a frozen embryo that is genetically identical

- **Preimplantation genetic diagnosis for sex selection except for sex-linked genetic diseases.**

  Several Panel members raised the concern that although the techniques used for preimplantation genetic diagnosis for sex selection are intended to prevent the suffering in children, most members were concerned that because such techniques have already been developed, there is no way to prevent them from being used for ethically unacceptable purposes (to select a fetus of a preferred sex). The Panel was not unanimous in its decision that this type of research is unacceptable. Those who did not support this prohibition did so because they believed that little can be done to prevent the unacceptable use of the technology while simultaneously protecting its ethically defensible uses. In general, however, the Panel believes it is valuable to make a strong statement that it finds Federal funding of the development of such technology for nontherapeutic sex selection unacceptable.

- **Development of human-nonhuman and human-human chimeras with or without transfer.**

  Although, technically speaking, the homologous chimeric state naturally exists in a few humans (e.g., certain hermaphrodites and persons with two blood types), the deliberate creation of chimeras is unacceptable because of deeply held beliefs about individuation and personal identity, as well as scientific concerns about the risks of transfer of such an embryo. Although some members of the Panel believe that some potential benefit could be gained from research involving human-human chimeras without transfer (e.g., lineage studies), the majority felt that the science and potential therapeutic applications are insufficiently convincing to allow human-human chimeric research to proceed under any conditions. This includes production of chimeras using human pluripotential embryonic stem cells. The Panel unanimously opposes, on ethical and scientific grounds, the creation of heterologous, or human-nonhuman chimeras, with or without transfer. As outlined in chapter 2, any resulting chimera would be a mixture of both cell types in all tissues, including the brain and gonads.

- **Cross-species fertilization except for clinical tests of the ability of sperm to penetrate eggs.**

  The Panel makes one exception to the prohibition against cross-species fertilization—the clinical use of hamster or similar eggs in the course of treatment of male infertility. These eggs are used to test the competence of a particular patient's sperm to penetrate an egg. The process has a clearly defined end point since the fertilized hamster eggs do not develop. Similar cross-species uses of human gametes in therapeutic and diagnostic contexts would also be permissible, as long as development does not proceed beyond the one-cell stage.

- **Attempted transfer of parthenogenetically activated human eggs.**

  Because it is not scientifically likely that a parthenogenetically activated oocyte could progress to a viable pregnancy, the Panel determined that there was little scientific merit to any such proposal. Even if a successful pregnancy were possible, the ethical complexities

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of bringing a parthenogenetic child to birth have not yet begun to be addressed. In addition, the Panel wishes to allay fears expressed by members of the public who are concerned about the end point of research on parthenogenesis. To many, this appears to represent a tampering with the natural order in unacceptable ways. By prohibiting the transfer of parthenotes, the Panel precludes any attempts to develop a fetus or child without a paternal progenitor.

- **Attempted transfer of human embryos in nonhuman animals for gestation.**

  The Panel overwhelmingly concluded to prohibit such research on the basis of scientific invalidity and moral opposition. There is every reason to believe that a human embryo would be immunologically rejected after transfer into another species or, at least, that maternal-fetal placental interactions would be profoundly affected. The risks to any children gestated in this way and the social issues involved are also totally unexplored.

  Studies of human gestation confirm the importance of maternal-fetal interactions during pregnancy. These are crucial not only for physiological development, but they also represent the beginnings of mother-child bonding and of human relationship. The Panel finds it repugnant to experiment with such relating between a human fetus and a nonhuman gestational mother. There is no justification for risking serious harm to the fetus and the child to be born.

- **Transfer of human embryos for extrauterine or abdominal pregnancy.**

  The potential benefits of establishing pregnancy outside the uterus for a woman who lacks a uterus are far outweighed by the risks to the child to be born and to the pregnant woman. However, excluding this type of research does not exclude research on extra-uterine pregnancies, which occur naturally at very low frequency in humans (e.g., intra-abdominal pregnancy).

Appendix A

Statement of Patricia A. King

Statement of Patricia A. King

Concurring in Part and Dissenting in Part

The Human Embryo Research Panel determined that permitting research on preimplantation human embryos within the scope of recommended guidelines is acceptable public policy. The report is attentive to and respectful of this society's diverse perspectives on the scientific, medical, and ethical dimensions of human embryo research. I believe that the report is exceptionally well reasoned in most of its recommendations, and I am pleased to have played a role in its development. I, however, am compelled to dissent from a few of the recommendations that concern fertilization of ova expressly for research purposes.

I agree with the Panel's conclusion that the creation of human embryos expressly for research purposes for the most serious and compelling of reasons is acceptable public policy. I reached this conclusion reluctantly, as did many of my fellow panelists, even though I do not believe that fertilization marks the beginning of human personhood. Nonetheless, fertilization marks a significant point in the process of human development, and the prospect of disconnecting fertilization from the rest of the procreative process in which there is intent to produce a child is profoundly unsettling. I am ultimately persuaded, however, that potentially beneficial information significant for the health and well-being of human persons might be gained by allowing fertilization of human ova when the research by its very nature cannot otherwise be conducted and the information needed cannot be obtained in any other manner. I believe that fertilization of ova for any other research purposes warrants further review. I dissent therefore from the Panel's recommendation that ova may be fertilized for research purposes in order to validate a study of potentially outstanding scientific and therapeutic value.

Allowing fertilization of oocytes expressly for research purposes offers potential for benefit to humankind, but it also raises fundamental ethical concerns. The prospect that humanity might assume control of life creation is unsettling and provokes great anxiety. The fertilization of human oocytes for research purposes is unnerving because human life is being created solely for human use. I do not believe that this society has developed the conceptual frameworks necessary to guide us down this slope. My concerns are heightened in the context of research activities where practices cannot be monitored easily by the public and where it is difficult to ascertain whether the research is being conducted responsibly.

At the very least, we should proceed with extreme caution. Perhaps the public's concerns can be allayed over time with the development of acceptable conceptual frameworks. In any event, the public must be convinced that such actions are necessary to obtain significant benefits for humankind and that the research will be responsibly conducted. In particular, the public should be assured that embryos will not be created because such creation is the most convenient means of answering important scientific questions that can be answered—perhaps more slowly—in other ways.

I do not believe that the goal of establishing scientific validity by using gametes from "normal" human controls provides a compelling reason to permit the fertilization of oocytes expressly for research. First, the need to validate experimental results by certain methodologies but not others is not easily understood by lay persons. Methodologies regarded by scientists as being the most effective may be viewed by nonscientists as problematic on ethical grounds. Second, the mere

assumption without more evidence that the number of spare embryos generated by couples in infertility treatment are inadequate to serve validation purposes is to my mind not compelling and carries us perilously close to fertilizing oocytes for no other reason than scarcity of spare embryos. Undoubtedly, using only spare embryos may delay research efforts, but, in these circumstances, I believe the delay is warranted. Finally, it is important to demonstrate that the fertilization of ova for research purposes is conducted responsibly before expanding its use.

Once the Panel agreed to permit fertilization of oocytes for purposes of research, it was faced with the task of deciding permissible sources of oocytes to be used for this purpose. I concur with the Panel's conclusions that women undergoing already scheduled surgery and women who agree to donate after death are permissible sources of oocytes. I would not permit, however, the use of oocytes from dead women where consent is obtained from next-of-kin or from women who are participants in infertility treatment.

Although allowing next-of-kin to consent to oocyte donation is consistent with generally accepted practices in organ and nongamete tissue donation, I believe that such practices are questionable with respect to donation of gametes. This is particularly true for the fertilization of gametes for research purposes. As the Panel recognizes, gamete tissue has special significance. Many persons will strongly object to gamete use in research. Others, if willing to donate in some circumstances, will object to the use contemplated here. Yet, such persons are not likely to object *explicitly* to donation because the possibility of gamete use is not widely appreciated. Moreover, I do not believe that arguments in favor of increasing the supply of organs and nongamete tissue in the context of therapeutic life-saving procedures through acceptance of next-of-kin permission are applicable here. These considerations lead me to conclude that respect for dignity and control over one's body demands that donation in this context require the woman's consent.

The Panel recognized for some purposes that some accepted practices in the organ donation context were not adequate when applied to gamete donation. I would have extended that logic to next-of-kin donation of oocytes for adult female cadavers as well. It is important to preserve public trust with respect to anatomical gifts.

The Panel also permits women who participate in infertility research to donate ova for fertilization for research purposes. I am not persuaded that women undergoing infertility treatment are likely to benefit directly as a result of donating oocytes, although the expectation that women with infertility problems as a group are likely to benefit is probably the case. To my mind, this possibility of benefit is outweighed by the vulnerability of women in infertility treatment, a matter acknowledged in the report. This vulnerability is especially worrisome, because clinical infertility practices are already heavily tinged with commercialism. It will be difficult to ensure that women in infertility treatment will not be subtly coerced or paid to donate even though the Panel has made clear that it objects to such practices.

Finally, the Panel's use of the terms "ex utero preimplantation embryo" or "preimplantation embryo" includes fertilized ova that have been flushed from a woman prior to implantation in her uterus and recognizes that such embryos are potential sources of embryos for research. The report, however, does not explicitly state that such embryos cannot be used in research where transfer is not contemplated. I would clearly prohibit such use, because the procedure, while infrequently used, does pose significant risks for women.

Appendix B

Statement of Carol A. Tauer

Statement of Carol A. Tauer

The question of whether the Panel ought to approve Federal funding of research involving the explicit fertilization of oocytes was resolved only after careful consideration, deliberation, and formulation. For reasons discussed in chapter 3, the Panel accepted research involving fertilization of oocytes under two carefully specified conditions. I believe that Federal funding of research should be acceptable only under these two conditions. Therefore, I strongly disagree with the Panel's decision to recommend "embryonic stem cell research that uses deliberately fertilized oocytes" for further review, rather than simply finding it unacceptable.

Because the issue of developing embryos for research is so morally sensitive and because of my concern that clear restrictions may be difficult to maintain, I believe that Federal funding should not be considered beyond the two conditions stated in chapter 3. These two conditions allow Federal funding only if the fertilization of oocytes is truly necessary in order to conduct the research project (either because the research of its very nature could not otherwise be conducted or because the very validity of the research requires the deliberate fertilization of oocytes). While there may be therapeutic reasons for developing cell lines of a vast variety of human genotypes, stem cell research studies do not require that cells be utilized from such a variety of genotypes. It would be only after research has demonstrated that the differentiated cells are therapeutically beneficial that one would want to ensure that people of different ethnic backgrounds are not deprived of therapy because of problems in matching transplantation antigens. Providing this variety of tissue types is a problem for tissue banks and distribution networks; it does not require federally funded research. The research itself can be conducted utilizing embryos that remain and are donated by couples who have completed their infertility treatment.

Given the Panel's desire to maintain clear limitation on the fertilization of oocytes for research purposes, I believe that the deliberate fertilization of oocytes in order to provide cells for embryonic stem cell research should be unacceptable for Federal research funding.

Appendix C

Statement of Bernard Lo

Statement of Bernard Lo

While human embryo research promises potential benefits, it also raises deep moral concerns. The Panel heard strong objections from citizens who believe that an embryo has the same moral standing as a child after delivery. I would like to express a different set of moral concerns. Human embryo research may raise fears that we are tampering inappropriately with nature, undermining respect for human life, or starting down slippery slopes that will end in unacceptable practices. These concerns are difficult to articulate, and people often use literary allusions, such as fears of *Frankenstein* or *Brave New World*.

Because of these concerns, I disagree with the recommendation on page 76 to allow research involving the use of existing embryos where one of the progenitors was an anonymous gamete source who received monetary compensation. This recommendation violates our ban on buying and selling gametes and embryos. We adopted this prohibition because regarding eggs, sperm, and embryos as commodities or property devalues human life. The exception in the case of existing embryos is defended because a retroactive ban would "present an unreasonable impediment to research." I am not persuaded by this argument because a future ban on payment to donors was regarded as reasonable. We should not give the impression that ethical guidelines may be overridden in order to make it easier to carry out research. Furthermore, preexisting embryos from anonymous donors may present problems with informed consent. We adopted the rule that donors must consent not only to the use of their gametes or embryos for research but also specifically to transfer or nontransfer of embryos to a uterus. According to our reasoning on page 53, we should exclude from research embryos whose gamete donors had not given such specific consent. It is likely that many anonymous, paid gamete donors assumed that their gametes would be transferred in utero and that some would object to using their gametes in experiments where transfer was not planned.

Research must not run ahead of moral reflection and policy guidelines. The public must be assured that human embryos will be accorded respect as potential persons, that research will be carried out in a careful and thoughtful manner, and that technological imperatives will not push the work beyond the bounds of moral acceptability. I believe this report is an important first step in providing such assurance.

Appendix D

Glossary and Diagrams

Glossary[1] and Diagrams

Amniocentesis: a procedure used for prenatal diagnosis at about 14 to 16 weeks of pregnancy. Fluid from the amniotic sac surrounding the fetus, which also contains fetal cells that have been shed during development, is sampled by a syringe inserted through the abdominal wall and uterus. The cells and fluid are used for chromosomal and biochemical testing.

Androgenote: a fertilized egg containing two sets of male chromosomes and no female chromosomes; usually arises from dispermic fertilization or fertilization by a diploid sperm and the subsequent exclusion of the female genetic contribution.

Asexual: having no sex or without sex.

Blastocyst: the developing preimplantation embryo, beginning about 4 days after fertilization. The blastocyst consists of a sphere made up of an outer layer of cells (the trophectoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).

Blastocyst division: also referred to as induced twinning. A single embryo at the blastocyst stage is mechanically divided into two so that each part receives an approximately equal number of trophoblasts and inner cell mass cells.

Blastomere: each of the cells produced when the fertilized egg cleaves into 2, then 4, 8, and 16 cells.

Blastomere separation: a technique by which the zona pellucida is removed from around a two- to eight-cell embryo, or morula, and the embryo is incubated in special solution so that the blastomeres separate and fall apart. The blastomeres are then cultured separately.

Chimera: an organism composed of cells derived from at least two genetically different zygotes, in theory possibly from separate species.

Choriocarcinoma: a malignant neoplasm of trophoblastic cells, formed by abnormal proliferation of the placental epithelium.

Chorionic villus sampling (CVS): a method of prenatal diagnosis undertaken as early as the ninth week of pregnancy. Fetal cells from chorionic villi (protusions of the membrane, called the chorion, that surround the fetus during early development) are suctioned out through the uterus and their DNA is analyzed.

Chromosomes: nucleic acid-protein structures in the nucleus of a cell. Chromosomes are composed chiefly of DNA, the carrier of hereditary information. Chromosomes contain genes, working

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[1] Some of the definitions were excerpted from *Embryo Experimentation: Ethical, Legal, and Social Issues* by P. Singer, H. Kuhse, S. Buckle, K. Dawson, and P. Kasimba (Cambridge: Cambridge University Press, 1990).

subunits of DNA that carry the genetic code for specific proteins, interspersed with large amounts of DNA of unknown function. A normal human body cell contains 46 chromosomes; a normal human gamete, 23 chromosomes.

Cleavage: the process of cell division in the very early embryo before it becomes a blastocyst.

Cloning: making genetically identical copies of a single cell or organism.

Complementary DNA (cDNA): DNA synthesized from a messenger RNA template; the single-strand form is often used as a probe in gene mapping.

Conceptus: the mass of cells resulting from the earliest stages of cell division of a zygote.

Congenital: existing at or before birth.

Cryopreservation: storage by freezing. Cryopreservation is used to store sperm and preimplantation embryos; similar methods are being developed for oocytes.

Cytoplasm: the contents of a cell other than the nucleus. Cytoplasm consists of a fluid containing numerous structures, known as organelles, that carry out essential cell functions.

Differentiation: the process whereby an unspecialized early embryonic cell acquires the features of a specialized cell such as a heart, liver, or muscle cell.

Diploid: a cell or tissue having two chromosome sets, as opposed to the haploid situation of gametes, which have only one chromosome set.

DNA: a chemical, deoxyribonucleic acid, found primarily in the nucleus of cells. DNA carries the instructions for making all the structures and materials the body needs to function.

Donor(s): an individual or couple who provide(s) sperm, eggs, gonadal tissue, or embryos.

Ectoderm: the upper, outermost of the three primitive germ layers of the embryo.

Egg: the mature female gamete; ovum.

Embryo: in humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus. See also **preimplantation embryo**.

Embryo biopsy: the removal of one or a few cells from the very early embryo for purposes of preimplantation genetic diagnosis.

Embryo transfer: the introduction of a preimplantation embryo into the uterus or fallopian tube. See **transfer**.

Embryonic disk: a group of cells, derived from the inner cell mass of the blastocyst, from which the later embryo and fetus will develop. The upper layer, or ectoderm, will ultimately give rise to skin, nerves, and brain, while the lower layer, or endoderm, will become lungs and digestive organs.

Mesoderm, a middle layer added in the process known as gastrulation, is the precursor to bone, muscle, and connective tissue. In humans, the embryonic disk is usually visible as part of the implanting blastocyst at the end of the second week of development.

Embryonic stem cells: primitive (undifferentiated) cells from the embryo that have the potential to give rise to a wide variety of specialized cell types.

Enucleated: a cell from which the nucleus has been removed.

Extracorporeal: situated outside the body.

Ex utero: outside the uterus.

Ex utero preimplantation embryo: a fertilized ovum in vitro that has never been transferred to or implanted in a uterus.

Fertilization: the process whereby male and female gametes unite; it begins when a sperm contacts the zona pellucida encasing the egg and ends with the formation of the zygote.

Fetus: in humans, the developing organism after the eighth week of gestation until birth. This stage is marked by the growth and specialization of organ function.

Follicle: the ovum and its encasing cells prior to ovulation.

Gamete: a mature sperm or egg.

Gastrulation: the process whereby the middle layer, or mesoderm, is added to the embryonic disk, leading to the primitive streak.

Gene: a working subunit of DNA. Each of the body's 100,000 genes carries the instructions that allow the cell to make one specific product such as a protein.

Genome: the complete genetic makeup of a gamete or cell.

Genomic imprinting: a biochemical phenomenon that determines, for certain specific genes, which one of the pair of identical genes, the mother's or the father's, will be active in that individual.

Genotype: the entire genetic constitution of an organism.

Germ cell: a sperm or egg, or a cell that can become a sperm or egg. All other body cells are known as somatic cells.

Germ-line genetic engineering: the introduction of genetic material into sperm, eggs, or fertilized eggs. The changes made by this introduction of genetic material may be inherited by offspring.

Haploid: a gamete having one chromosome set, as opposed to the diploid situation of cells or tissues, where there are two chromosome sets.

Hormone: a substance produced by an organ or cell that acts specifically on another organ.

Hydatidiform mole: a tumor, generally benign, that can develop from an abnormal preimplantation embryo that carries chromosomes only from the father.

Hyperstimulation syndrome: excessive response to the administration of ovulation-inducing agents that are used in the treatment of some cases of infertility.

Implantation: attachment of the blastocyst to the lining of the uterus and its subsequent embedding in the endometrium. Implantation begins about 5 to 7 days after fertilization and is complete by 12 to 14 days after fertilization.

Individuation: the point at which the embryo proper is determined to be a distinct developing individual.

Infertile: unable to have children. Specialists define infertility as the inability to conceive after 12 months of intercourse without contraception.

Inner cell mass: the cluster of cells inside the blastocyst, which gives rise to the embryonic disk of the later embryo and ultimately the fetus.

Integrins: adhesive proteins that play a role in implantation of the embryo in the uterus.

Interspecies: used to describe the offspring resulting from the mating of two different species of organisms, i.e., interspecies hybrids.

In utero: in the uterus.

In vitro: literally, "in glass"; in a laboratory dish or test tube; an artificial environment.

In vitro fertilization (IVF): an assisted reproduction technique in which fertilization is accomplished outside the body.

In vivo: in the living subject; a natural environment.

Laparoscopy: a method used for collecting eggs for IVF that involves the insertion of an optical scanner (laparoscope) through a small incision in the abdominal wall; a small tube is also inserted for the removal of the eggs.

Mesoderm: the middle of the three primary germ layers of the embryo.

Metastasis: the transfer of disease from one organ or part of the body to another not directly connected with it because of the transfer of pathogenic microorganisms or of cells; all malignant tumors are capable of metastasizing.

Mitochondria: small, spherical to rod-shaped components (organelles) of the cytoplasm; they are the principal sites of the generation of energy resulting from the oxidation of foodstuffs.

Morula: the compact sphere created when a developing preimplantation embryo grows to 12 to 16 blastomeres, about 3 or 4 days after fertilization.

Mosaic: an individual derived from a single zygote that is composed of two or three groups of cells that have developed genetic differences, who thus displays variegated characteristics.

Mutation: a change in DNA that alters a gene and thus the gene's product, leading in some cases to deformity or disease. Mutations can occur spontaneously during cell division or can be triggered by environmental stresses such as sunlight, radiation, and chemicals.

Neurulation: the beginning of the formation of the embryonic nervous system, at about 18 days in the human. A flat plate of ectodermal cells (the neural plate) rolls up into a hollow tube. Errors in neurulation can give rise to neural tube defects, in which the brain and/or spinal cord is exposed.

Nuclear transplantation: a type of cloning in which the nucleus from a blastomere is fused with an egg from which the nucleus has been removed. The DNA of the transplanted nucleus thus directs the development of a resulting embryo.

Nucleus: the cell structure that houses the chromosomes.

Oocyte: the immature female gamete or germ cell.

Oophorectomy: excision of one or both ovaries.

Ovulation: the release of a mature egg from the ovary.

Ovum: the mature female germ cell; the egg.

Parthenogenesis: the activation of an egg so that it begins to develop in the absence of sperm.

Parthenote: an activated oocyte.

Preembryo: alternative name for the preimplantation embryo. See **preimplantation embryo**.

Preimplantation embryo: the very early, free-floating embryo, from the time the egg is fertilized until implantation in the mother's womb is complete, about 12 to 14 days after fertilization. See **ex utero preimplantation embryo**.

Preimplantation genetic diagnosis: See **embryo biopsy**.

Primitive streak: an advancing groove that develops along the midline of the embryonic disk. Its appearance during gastrulation, about 14 to 15 days after fertilization, coincides with mesoderm formation. A milestone in embryo development, the primitive streak establishes and reveals the embryo's head-tail and left-right orientations.

Pronuclei: the egg nucleus and the sperm nucleus, after the sperm has penetrated the egg but before the two nuclei have commingled their chromosomes.

Sentience: strictly, the ability to sense something; in ethics the term is normally used to refer to the ability to feel (at least) pain.

Sex-linked: a special case of linkage occurring when a gene that produces a certain phenotypic trait is located on the X chromosome; also referred to as X-linked.

Spare embryo: a term sometimes used to describe an embryo produced through IVF treatment that is in excess of the number acceptable for transfer to the woman.

Species: group of individuals capable of interbreeding to produce fertile offspring.

Sperm (spermatozoa): mature male reproductive cells.

Stem cells: See **embryonic stem cells**.

Syngamy: the final stage in fertilization in which chromosomes from the male and female gametes come together to form the zygote.

Teratogen: an agent that raises the incidence of congenital malformations.

Totipotent: having unlimited capability. The totipotent cells of the very early embryo have the capacity to differentiate into extraembryonic membranes and tissues, the embryo, and all postembryonic tissues and organs.

Transfer: see **embryo transfer**.

Trophectoderm cells: cells that make up the outer layer of the developing blastocyst and will ultimately form the embryonic side of the placenta. They are precursors to trophoblast cells.

Trophoblast: extraembryonic tissue responsible for negotiating implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.

Twinning: see **blastocyst division**.

Uterine flushing: the procedure of washing the recently formed embryo from a woman's fallopian tube or uterus before implantation has occurred.

Uterus: the female reproductive organ in which the embryo develops.

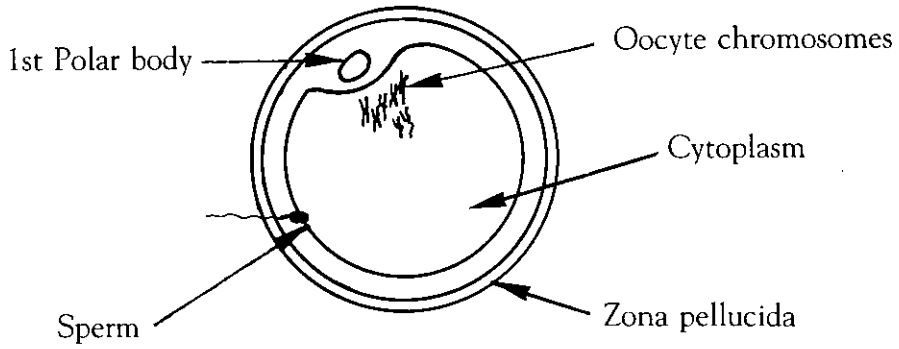
X-inactivation: the process by which one of the two X chromosomes in the female is inactivated during normal development.

X-linked: see **sex-linked**.

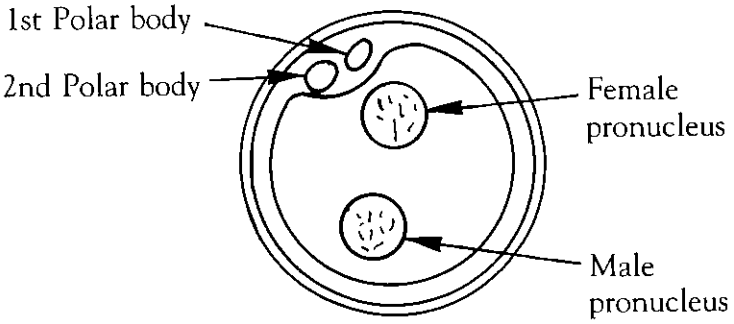
Zona pellucida: the outer coating of the egg cell, which continues to surround the preimplantation embryo until about 4 or 5 days after fertilization.

Zygote: the single-celled, fertilized egg.

Summary of fertilization

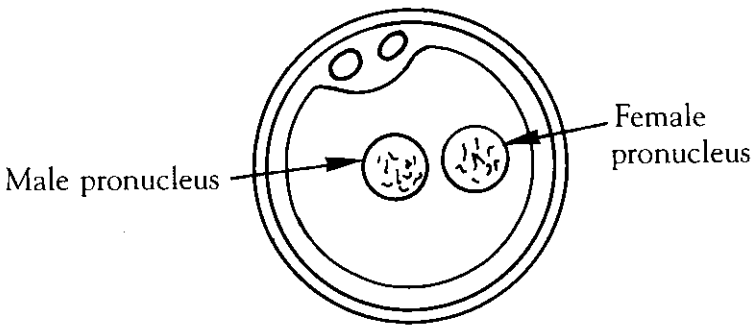


A sperm begins to enter the oocyte



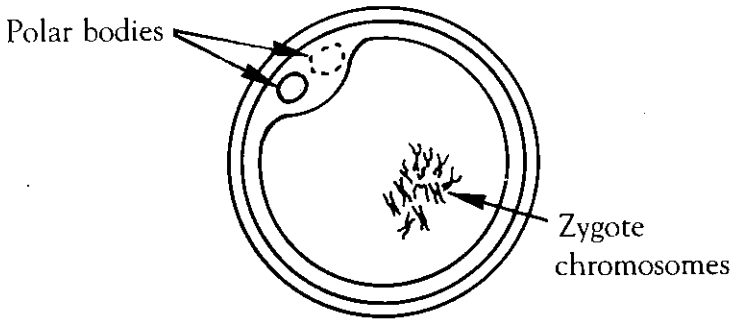
AFTER 9–12 HOURS

Two pronuclei are clearly visible within the oocyte; one from the sperm and one from the oocyte.



AFTER 10–22 HOURS

The chromosomes in each pronucleus are drawn together by microtubules in the cytoplasm.

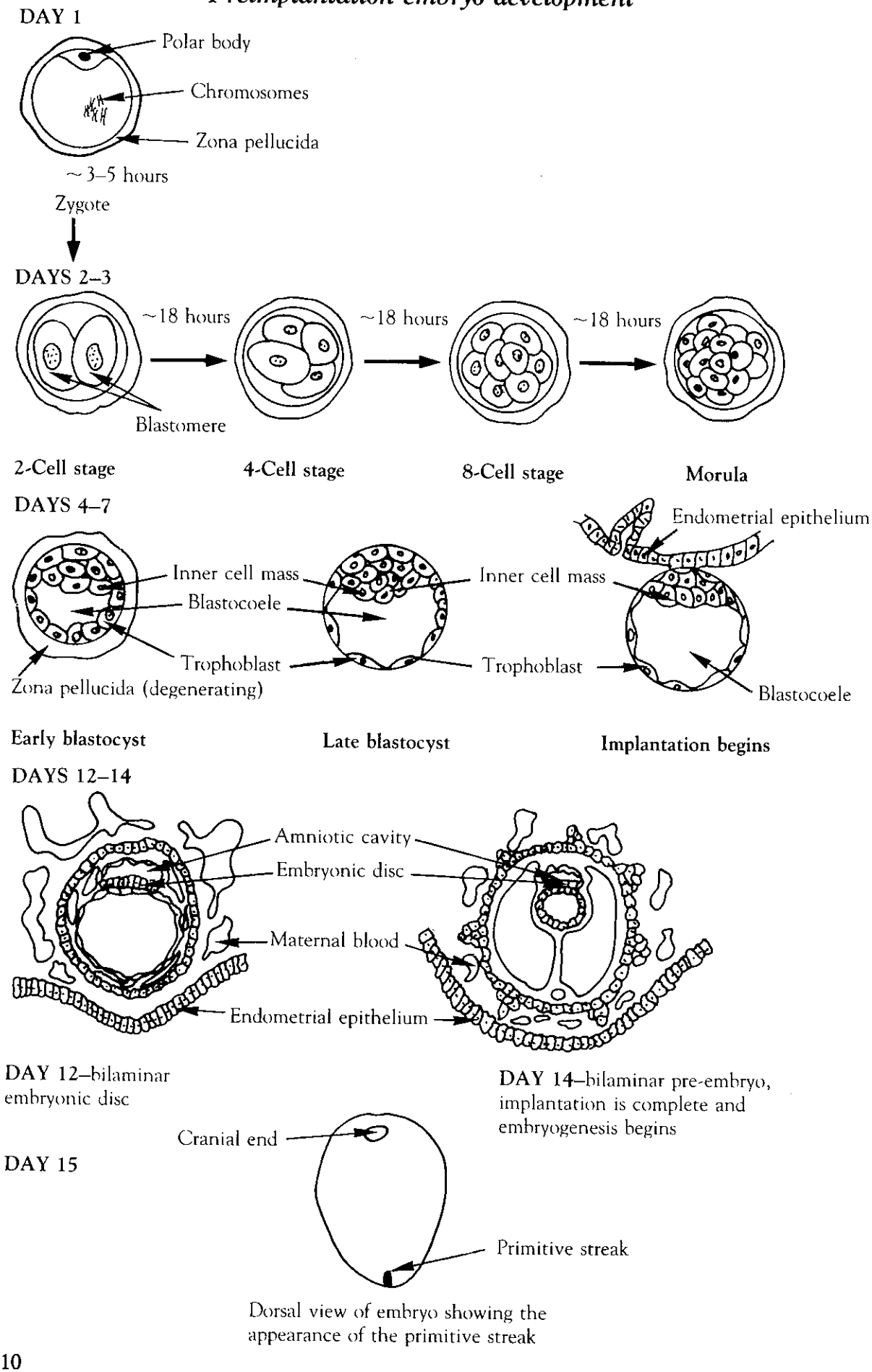


22–30 HOURS

The chromosomes of the sperm and oocyte are combined and syngamy is complete. In 1–3 hours the zygote will undergo the first cleavage division.

Source: Peter Singer, et al. (eds), Embryo Experimentation (Cambridge: Cambridge University Press, 1990)

Preimplantation embryo development



Source: Peter Singer, et al. (eds), Embryo Experimentation (Cambridge: Cambridge University Press, 1990)

Appendix E

Panel Meeting Agendas

Panel Meeting Agendas

NIH HUMAN EMBRYO RESEARCH PANEL

February 2–3, 1994
Bethesda Marriott Hotel
5151 Pooks Hill Road
Bethesda, Maryland

Wednesday, February 2, 1994

9:00 a.m. - 9:15 a.m.	Opening Remarks/Review of Panel Charge/Introduction of Overall Chair and Co-chairs
	Harold Varmus, M.D., Director, NIH
9:15 a.m. - 9:30 a.m.	Introduction of Panel Members
	Steven Muller, Ph.D., Overall Chair
9:30 a.m. - 10:30 a.m.	Historical Review of Federal Policy on Human Embryo Research
	Gary Ellis, Ph.D., Director, NIH Office of Protection From Research Risks
	F. William Dommel, Jr., J.D., Senior Policy Advisor, NIH Office of Protection From Research Risks
10:30 a.m. - 10:45 a.m.	Coffee Break
10:45 a.m. - 12:00 p.m.	Discussion of Panel's Charge
12:00 p.m. - 1:00 p.m.	Lunch
1:00 p.m. - 3:00 p.m.	State of the Science of Human Embryo Research
	Jonathan Van Blerkom, Ph.D., Department of Molecular, Cellular and Developmental Biology, University of Colorado
	Discussion

3:00 p.m. - 5:00 p.m.	Public Comment Session
5:30 p.m. - 7:00 p.m.	Reception/Dinner for Panel

Thursday, February 3, 1994

8:30 a.m. - 10:30 a.m.	Review of International Guidelines Governing Human Embryo Research and Relevant State Laws
	Lori B. Andrews, J.D., Visiting Professor, Kent-Chicago College of Law
	Discussion
10:30 a.m. - 10:45 a.m.	Coffee Break
10:45 a.m. - 12:45 p.m.	Review of Ethical Issues Raised by Human Embryo Research
	Bonnie Steinbock, Ph.D., Department of Philosophy, State University of New York, Albany
	Discussion
12:45 p.m. - 1:30 p.m.	Lunch
1:30 p.m. - 4:30 p.m.	Discussion of Approach to Panel's Charge and Determination of Content/Dates of Future Meetings

Adjourn

NIH HUMAN EMBRYO PANEL MEETING

March 14, 1994
Bethesda Marriott Hotel
5151 Pooks Hill Road
Bethesda, Maryland

8:30 a.m. - 8:35 a.m.	Welcome and Opening Comments *Dr. Muller*
8:35 a.m. - 9:05 a.m.	Review of Panel's Interim Progress on Formulation of Issues Science Issues and Ethical/Public Policy Perspectives Identified by Science Work Group *Dr. Hogan* Ethical/Public Policy Issues and Science Perspectives Identified by Policy Work Group *Ms. King*
9:05 a.m. - 10:15 a.m.	Scientific Presentations on Opportunities and Potential Benefits of Research Involving the Human Embryo New Developments, Technologies, and Opportunities in Preimplantation Genetic Diagnosis *Dr. Hughes* Developmental Biology of Embryos and Embryonic Stem Cells: Current Understanding and Potential Applications *Dr. Hogan* Advances in Murine Oocyte Maturation Technologies and Implications for Enhancing Fertilization Potential *Dr. Eppig* *(Dr. Eppig's presentation will include information on parthenogenesis.)*
10:15 a.m. - 10:30 a.m.	Coffee Break
10:30 a.m. - 11:30 a.m.	Panel Discussion of Scientific Presentations

11:30 a.m. - 12:30 p.m.	Deliberative Session
	Continuation of Formulation of Science Issues
	Dr. Hogan
	Continuation of Formulation of Policy Issues
	Ms. King
12:30 p.m. - 1:30 p.m.	Lunch
1:30 p.m. - 3:30 p.m.	Public Comment Session
3:30 p.m. - 3:45 p.m.	Coffee Break
3:45 p.m. - 4:30 p.m.	Panel Discussion
	Insights and Perspectives of a Former Director of the NIH Office of Protection from Research Risks and Staff Director of the Ethics Advisory Board 1978-1980
	Dr. Charles McCarthy
4:30 p.m. - 6:30 p.m.	Deliberative Session
	Continuation of Formulation/Elucidation of Issues, Classification of Areas of Research, and Development of Guidelines
6:30 p.m. - 7:00 p.m.	Wrap-up Panel Assignments Development of Next Meeting Agenda

Adjourn

NIH HUMAN EMBRYO PANEL MEETING

April 11–12, 1994
Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

Monday, April 11, 1994

8:30 a.m. - 8:35 a.m.	Welcome and Opening Comments *Dr. Muller*
8:35 a.m. - 10:30 a.m.	Deliberative Session I: Discussion of Draft Panel Recommendations On Issues Related to Moral Status of the Human Embryo and Acceptability of Areas of Human Embryo Research *What are the competing ethical frameworks with respect to the moral status of the embryo? What framework should guide the Panel in its deliberations? What, if anything, should the Panel say about the status of gametes? What should be the Panel's recommendation about the acceptability of embryo research from gastrulation (the process that begins with the formation of the primitive streak) on? What, if anything, should the Panel say about research on embryos that will not be transferred?* Discussants: *Dr. Green, Dr. Hendrickx, Dr. Hogan, Dr. Tauer*
10:30 a.m. - 10:45 a.m.	Coffee Break
10:45 a.m. - 11:30 a.m.	Continuation of Deliberative Session I
11:30 a.m. - 12:30 p.m.	Deliberative Session II: Discussion of Draft Panel Recommendations on Issues Related to Ethically Acceptable Sources of Human Embryos and Oocytes *What are the possible sources of embryos (include a discussion of sources of ova, such as IVF programs, surgical procedures, healthy adult volunteers, fetuses, neonates, etc.)? What, if any, restrictions should be placed on sources of embryos or oocytes? Where it is permissible to use embryos or oocytes, what informed consent issues and payment issues need to be considered?* Discussants: *Dr. Lo, Ms. Aronson, Dr. Eppig, Dr. Guerra, Dr. Martin, Dr. Murray, and Prof. Nelkin*

12:30 p.m. - 1:30 p.m.	Lunch
1:30 p.m. - 3:00 p.m.	Continuation of Deliberative Session II
3:00 p.m. - 3:15 p.m.	Coffee Break
3:15 p.m. - 5:15 p.m.	Public Comment Session
5:15 p.m. - 6:45 p.m.	Deliberative Session III: Discussion of Draft Panel Recommendations on Appropriate Mechanisms/Levels of Review

What, if any, additional mechanisms are required to evaluate and monitor embryo research at a national or local level with respect to acceptable embryo research and to embryo research that should await further discussion?

Discussants: *Ms. Charo, Dr. Donahoe, Dr. Hughes, Dr. Huntley, Dr. Keohane, and Dr. Ryan*

Tuesday, April 12, 1994

8:30 a.m. - 10:30 a.m.	Deliberative Session IV: Review of Any Outstanding Issues in Three Major Issue Areas*

Discussants: *Dr. Green, Dr. Lo, and Ms. Charo*

10:30 a.m. - 10:45 a.m.	Coffee Break
10:45 a.m. - 11:45 a.m.	Deliberative Session V: Discussion of Additional Ethical/Policy Issues That Need To Be Addressed and Panel Assignments

Ms. King

11:45 a.m. - 12:15 p.m.	Review of Outline of Major Scientific Issues: Development of Additional Areas

Dr. Hogan

12:15 p.m. - 12: 30 p.m.	Wrap-up

Adjourn

**The purpose and content of this session may change as necessary.*

NIH HUMAN EMBRYO PANEL MEETING

May 3-4, 1994
Holiday Inn Bethesda
Versailles IV
8120 Wisconsin Avenue
Bethesda, Maryland

Tuesday May 3, 1994

9:00 a.m. - 9:05 a.m.	Welcome and Opening Comments *Dr. Muller*
9:05 a.m. - 10:15 a.m.	Review of Preliminary Draft Conclusions and Guidelines on Overarching General Principles (Draft chapter 7, pages 1-2) *Dr. Muller*
10:15 a.m. - 10:30 a.m.	Coffee Break
10:30 a.m. - 12:00 p.m.	Review of Preliminary Draft Conclusions and Guidelines on Research Involving Ex Utero Human Embryos Intended for Implantation (Draft chapter 7, pages 2-4) *Ms. King*
12:00 p.m. - 1:00 p.m.	Lunch
1:00 p.m. - 3:00 p.m.	Review of Preliminary Draft Conclusions and Guidelines on Research Involving Ex Utero Human Embryos Not Intended for Implantation (Draft chapter 7, pages 4-7) *Ms. King*
3:00 p.m. - 3:15 p.m.	Coffee Break
3:15 p.m. - 5:00 p.m.	Review of Preliminary Draft Conclusions and Guidelines on Research Involving Parthenogenesis (Draft chapter 7, pages 7-8), on Research Requiring Additional Review (Draft chapter 7, pages 9-10) and on Research That Should Not Be Supported (Draft chapter 7, pages 9-10) *Ms. King*

Wednesday, May 4, 1994

9:00 a.m. - 11:00 a.m.	Public Comment Session
11:00 a.m. - 11:15 a.m.	Coffee Break
11:15 a.m. - 12:00 p.m.	Review of Preliminary Draft of Scientific and Medical Considerations in Human Embryo Research (Draft chapter 2) *Dr. Hogan*
12:00 p.m. - 1:00 p.m.	Lunch
1:00 p.m. - 2:00 p.m.	Review of Preliminary Draft of Views of Moral Status of Human Embryo and Ethical Frameworks for Consideration of Human Embryo Research (Draft chapters 3 and 4) *Dr. Green*
2:00 p.m. - 3:00 p.m.	Review of Preliminary Draft of Sources of Gametes and Embryos and Informed Consent and Commercialization Issues (Draft chapter 5) *Dr. Lo*
3:00 p.m. - 3:15 p.m.	Coffee Break
3:15 p.m. - 4:30 p.m.	Review of Preliminary Draft of Review and Oversight of Human Embryo Research (Draft chapter 6) *Ms. Charo*
4:30 p.m. - 5:00 p.m.	Writing Assignments Next Steps

Adjourn

NIH HUMAN EMBRYO PANEL MEETING

June 21-22, 1994
Holiday Inn Bethesda
Versailles I
8120 Wisconsin Avenue
Bethesda, Maryland

Tuesday, June 21, 1994

9:00 a.m. - 9:10 a.m.	Welcome and Opening Comments *Dr. Muller*
9:10 a.m. - 10:00 a.m.	Structure and Organization of Report *Dr. Muller*
10:00 a.m. - 10:15 a.m.	Coffee Break
10:15 a.m. - 12:00 p.m.	Review and Deliberation of Outstanding Policy Issues *Ms. King*
12:00 p.m. - 1:00 p.m.	Lunch
1:00 p.m. - 1:45 p.m.	Continuation of Review and Deliberation of Outstanding Policy Issues *Ms. King* Review and Deliberation of Outstanding Scientific Issues *Dr. Hogan*
1:45 p.m. - 2:45 p.m.	Review of Draft Chapter 2 *Dr. Hogan*
2:45 p.m. - 3:00 p.m.	Coffee Break
3:00 p.m. - 5:10 p.m.	Public Comment Session

Wednesday, June 22, 1994

9:00 a.m. - 10:30 a.m.	Discussion of Draft Chapter 6
	Ms. Charo and Ms. King
10:30 a.m. - 10:45 a.m.	Coffee Break
10:45 a.m. - 12:00 p.m.	Review of Draft Chapter 5
	Dr. Lo
12:00 p.m. - 1:00 p.m.	Lunch
1:00 p.m. - 1:30 p.m.	Continuation of Review of Draft Chapter 5
	Dr. Lo
1:30 p.m. - 4:00 p.m.	Review of Draft Chapters 3 and 4
	Dr. Green and Dr. Tauer
4:00 p.m. - 4:45 p.m.	Review of Draft Chapters 7 and 1
	Dr. Muller
4:45 p.m. - 5:00 p.m.	Next Steps

Adjourn

NIH HUMAN EMBRYO PANEL MEETING

September 27, 1994
National Institutes of Health
Building 31, Conference Room 10
9000 Rockville Pike
Bethesda, Maryland

9:30 a.m. - 9:40 a.m.	Opening Comments from the NIH Director *Dr. Varmus*
9:40 a.m. - 9:50 a.m.	Opening Comments from the Panel Chair *Dr. Muller*
9:50 a.m. - 10:10 a.m.	Review of Panel's Scientific Findings *Dr. Hogan*
10:10 a.m. - 10:55 a.m.	Review of Panel's Public Policy Conclusions and Recommendations *Ms. King* Ethical Considerations in Preimplantation Human Embryo Research *Dr. Green* Sources of Gametes and Embryos for Research *Dr. Lo* Principles and Guidelines for Preimplantation Human Embryo Research and Categories of Preimplantation Human Embryo Research *Ms. King*
10:55 a.m. - 11:25 a.m.	Comments by Each Panel Member
11:25 a.m. - 11:30 a.m.	Closing Comments and Next Steps *Ms. Chamblee and Dr. Alexander*

Adjourn

11:40 a.m. - 12:30 p.m. Media Availability

Appendix F

Presenters During Public Comment Sessions

Presenters During Public Comment Sessions

February 2–3

Frederick O. Bonkovsky, Ph.D.
Director, Bioethics Program
Clinical Center, NIH
Bethesda, MD

Maria Bustillo, M.D.
Board Member, Society for the Advancement of Women's Health Research
Washington, DC

Cynthia Cohen, Ph.D., J.D.
National Advisory Board on Ethics in Reproduction
Washington, DC

Richard Doerflinger, M.A.Div.
Associate Director, Secretariat for Pro-Life Activities
National Conference of Catholic Bishops
Washington, DC

Matthew Habiger, O.S.B., Ph.D.
Executive Director, Human Life International
Gaithersburg, MD

Ms. Lynne Lawrence
Director, Government Relations
American Fertility Society
Washington, DC

William May, Ph.D.
Professor of Moral Theology,
John Paul II Institute
Pope John XXIII Medical Moral Research Center
Washington, DC

Charles McCarthy, Ph.D.
Board Member, Public Responsibility in Medicine and Research
Boston, MA

Claire Nader, Ph.D.
Chair, Council for Responsible Genetics
Cambridge, MA

Mr. Rick Sellers
Potomac, MD

Ms. Jolene Hall Slotter
Bethesda, MD

March 14

Stephen Coles, M.D., Ph.D., and Ms. Laurie Coles
Arlington, VA

Olga Fairfax, Ph.D.
Wheaton, MD

Dianne Irving, Ph.D.
Bethesda, MD

Ms. Kathy May
Vice President, Fragile X Research Foundation
Fairfax, VA

Ms. Wendy McGoodwin
Program Director, Council for Responsible Genetics
Cambridge, MA

Patrick Norris, O.P.
Associate Director, Center for Health Care Ethics
St. Louis University Health Sciences Center
St. Louis, MO

Ms. Karen Shprintz-Grossman
Silver Spring, MD

April 11–12

Ms. Judith Aungst
Delaware Pro-Life Coalition, Inc.
Wilmington, DE

Ms. Cecelie Blakey
Washington, DC

Ms. Doris Gordon
National Coordinator, Libertarians for Life
Wheaton, MD

Pastor Jerry Horn
Vice President, American Life League
Stafford, VA

Jean-Francois Orsini, Ph.D.
President, Washington-Metro Chapter
Society of Catholic Social Scientists
Washington, DC

Robert Weise, Ph.D.
Chair, Pastoral Ministry and the Life Sciences (Concordia Seminary, St. Louis)
Representing the Lutheran Church Missouri Synod
St. Louis, MO

May 3–4

Robert C. Cefalo, M.D., Ph.D.
Chair, Committee on Ethics
American College of Obstetricians & Gynecologists
Washington, DC

Marco Colombini, Ph.D.
Sandy Spring, MD

Marianne Dellatorre, M.D.
North Bethesda, MD

Ms. Serrin M. Foster
Executive Director, Feminists for Life of America
Washington, DC

Ms. Kathleen Gettis
Levittown, PA

George Isajiw, M.D.
Past President, National Federation of Catholic Physicians' Guilds
Upper Darby, PA

Craig Kliger, M.D.
Member, Council on Ethical & Judicial Affairs
American Medical Association
Chicago, IL

Mary Faith Marshall, Ph.D.
Director, Program in Biomedical Ethics
(Medical University of South Carolina)
Representing Charleston Health Care Colloquium
Charleston, SC

R. Martin Palmer, Jr., Esq.
Hagerstown, MD

Mr. Paul Soberman
Brooklyn, NY

Mr. John J. Watson
Levittown, PA

Ms. Katherine Watt
Allentown, PA

June 21–22

Ms. Cindy Conry
Mokena, IL

Ms. Linda DeBenedictis
State Coordinator and President, New England
Patients' Rights Group
Norwood, MA

Mr. and Mrs. Paul DeCamara
Ft. Washington, PA

Richard Doerflinger, M.A.Div.
Associate Director, Secretariat
for Pro-Life Activities
National Conference of Catholic Bishops
Washington, DC

Ms. Linda Kaplan
Midlothian, VA

William Mahoney, Esq.
West Roxbury, MA

Msgr. Thomas J. Scanlon
Philadelphia, PA

Edward Sheridan, M.D.
Associate Clinical Professor
Georgetown Medical School
Washington, DC

Margaret Stucki, Ph.D.
(represented by Olga Fairfax, Ph.D.)
Pocatello, ID

Robert White, M.D., Ph.D.
Professor of Surgery
Director of Neurosurgery and
the Brain Research Laboratory
Case Western Reserve University
Cleveland, OH

Appendix G

Titles of Commissioned Papers

Titles of Commissioned Papers

The following papers, which appear in volume II of this report, were commissioned by the NIH to provide background information to the Panel.

"The History, Current Status and Future Direction of Research Involving Human Embryos" by Jonathan Van Blerkom, Ph.D.

"Ethical Issues in Human Embryo Research," by Bonnie Steinbock, Ph.D.

"Cross-Cultural Analysis of Policies Regarding Embryo Research," by Lori B. Andrews, J.D., and Nanette Elster

"State Regulation of Embryo Research," by Lori B. Andrews, J.D.