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An Incremental Approach to NBAC Deliberation on Human Pluripotential Stem Cells (PSC) Research

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I. Introduction

This paper will: 1) describe the scope of the tasks of a "thorough" NBAC review of PSC research, 2) discuss an incremental approach to these tasks, with strengths and weaknesses, and 3) make recommendations to NBAC.

A. Three Areas of Ethical and Public Policy Concern

Research with PSCs raises at least three ethical and public policy concerns:

1) Sources of PSCs

Is it morally acceptable to derive PSCs for research from all possible sources? Are such activities acceptable for federal funding?

2) Uses of PSCs in research

Are are all present and prospective uses of PSCs for research morally acceptable? Are such activities acceptable for federal funding?

[Note: Ethical concern about "uses" will heighten at the threshold of clinical trials of cell-directed therapies in humans. The scientific foundations for PSC based therapy have yet to be laid. Mouse research is the main source of clinically interesting information. Replicable therapeutic research in higher animals is needed. Leading scientists (Thomson, Hogan) predict a 5 year period to reach this threshold.]

3) Effects on science of the ban on research with human embryo research:

The ban infringes on societal values and distributive justice by limiting optimal NIH involvement not only in this promising scientific and therapeutic area -- PSC research leading to cell directed therapy -- but in many other areas of infertility and genetic research. The Thomson/Gearhart reports changed the context. Relevant here are issues of respect for excess embryo donors, fairness to taxpayers, fairly distributing the benefits and burdens of embryo research, and closing the gap between diagnosis (can diagnose anything) and therapy (can treat very little) in the Human Genome Project.

B. Sources for deriving PSCs. The sources: (ranked --in my view -- in order of legal/moral acceptability and degree of moral controversy).

1. PSCs derived from human fetal tissue following elective abortion (Gearhart research).

2. PSCs derived from human embryos "donated for research" (by parents); these are embryos in excess of clinical needs to treat infertility by IVF (Thomson research).

3. PSCs to be derived from human (or hybrid) embryos generated asexually by somatic cell nuclear transfer (using enucleated human or animal ova).

4. PSCs to be derived from human "research" embryos created from donor gametes for the sole purpose of research.

C. Proposed studies using PSCs. The uses of the research:

1) Understanding the similarities and differences between PSCs grown from blastocysts and PSCs grown from fetal germ cells.

2) understanding cellular differentiation, etc.

3) using cell lines grown from PSCs for drug development.

4) therapeutic uses - cellular transplants from donor cell banks, with or without genetic alteration to prevent or ameliorate graft-vs.-host disease (GVHD).

5) therapeutic uses - using genetically altered cells with somatic cell nuclear transplant (cloning technology) to grow cells to return to patient, thus avoiding GVHD.

6) therapeutic uses - other PSC-assisted gene therapy (Austin Smith testimony, NIH cloning paper 4-27-98), including PSC-assisted germline genetic transfer (Parens testimony).

II. The Tasks of the NBAC

A. NBAC has three tasks in regard to ethical and public policy issues in PSC research:

1) to clarify the ethical considerations relevant to deriving PSCs for research. NBAC must choose whether to focus on derivation from each source (I. B. 1-4) or focus on the sources which have been reported to date, i.e., I. B. 1-2.

2) to articulate consensus ethical standards to guide policy; i.e., what standards ought to guide public policy for federal

funding of PSC research.

3) to recommend safeguards to contain or prevent abuses that have occurred or that could occur when and if policy is implemented.

The President requested NBAC's "thorough review" of the issues associated with PSC research, including a source from hybrid embryos resulting from animal egg/human somatic cell fusion. The issue: "How thorough is thorough?" must be raised, especially if NBAC wants a report by June 1, 1999. A literally "thorough" review would require completing each of the three tasks above for all of the sources/issues in (I.B.) and (I.C.) above), including Parens' argument for what is in the "big picture," i.e., how PSC research converges into the longstanding debate about human germline gene transfer. This task cannot be done in the time frame proposed. Also, other groups (AAAS Taskforce & RAC) are examining intentional and unintentional germline gene tranfer. An alternative approach may fit the NBAC's tasks and timeline better.

III. An Incremental Approach: Strengths and Weaknesses

This section is on the strengths and weaknesses of an incremental or case-by-case approach to NBAC's tasks to review PSC research. Its familiarity to those who work in science, law, or ethics is one strength of this approach. When presented with several cases (or experiments), which on their face, seem similar or in the same family of cases, one proceeds incrementally, or case-by-case. Beginning with the most "settled" case (or in science with the most proven experiment), one then works outward, case by case, to consider each case until one reaches the least settled, most problematic and controversial cases. The task is to search for moral judgments (and the principles that guide these judgments) that hold from case to case, as well as for features of cases that make them so dissimilar that one would say that they do not belong to that "family" or "line" of cases. In ethics, this approach is known as case-based or casuistical reasoning. The remainder of this section takes the reader through a brief discussion of an incremental approach to these cases.

NBAC (and the nation) is faced with a group of cases or situations in which PSCs can be derived and used in research. How should NBAC morally deliberate about these cases? Working incrementally, NBAC must keep its three tasks in mind: first, it will seek to identify the clearest and most defensible moral principles or rules that guide action from case to case (or where cases are so different as to require different moral guidance); secondly, it will show (by consensus) how these principles and rules can guide public policy, and thirdly, it will propose safeguards and guidelines to prevent abuses.

Case 1. The most settled case: I. B. 1. (deriving PSCs from fetal tissue after elective abortion). The moral controversies associated with fetal tissue transplantation research were hotly debated in the 1980s and 1990s. Sufficient areas of moral consensus emerged through democratic processes to embody them in P.L. 103-43, appropriately named "The Research Freedom Act."

Moral principles and rules:

a) beneficence based; i.e., (although still contested by some) society should not forgo the therapeutic benefits to persons of transplant uses of fetal tissue obtained after legal elective abortions;

b) autonomy based; i.e., society should respect the altruism of donating fetal tissue for research expressed by women who have made legal abortion decisions;

c) nonmaleficence based; to prevent the effects of fetal tissue transplant research from widening the social practice of elective abortion, these rules are required: the consent process about abortion decisions must precede and be conducted separately from the consent process to donation of fetal tissue for transplant research; prohibited are designated donation, monetary inducements to women undergoing abortion, and buying or selling fetal tissue;

d) prudential concerns: payments are permitted to transport, process, preserve, or implant fetal tissue, or for quality control and storage of such tissue.

A thorough review of this case would cover the findings of the Human Fetal Tissue Transplantation Research Panel (1990), the history of the "indefinite" moratorium, and the legislative history of PL 103-43, 1993. The DHHS General Counsel has already stated (Jan. 15, 1999) that NIH can fund research to derive the PSCs from fetal tissue, as long as the requirements of Public Law 103-43 are followed. Fetal tissue transplant research has been funded, without significant incident, by the NIH for several years. The NIH has guidelines for this research, but the focus is on transplant research and not PSCs. NBAC can build on the history of fetal tissue transplant research to recommend guidelines for deriving and using PSCs from fetal tissue for research.

These considerations of Case 1 are clearly not beyond moral challenge by a view condemning most elective abortions on moral grounds as unfair to the fetus. This view also claims that researchers are morally complicit with abortions that kill fetuses.

A thorough review will revisit the complicity issue: is the researcher in Case 1 morally "complicit" in the abortion act itself? This society permits cadaver organ and tissue donation,

abortion, and donation of fetal tissue for research. Society encourages donation of cadaver organs for transplantation, and some organs result from suicides or vehicular homicides, yet no one argues that physicians are "complicit" in these causes of death. The claim of complicity arises from condemnation of abortion practices based on moral absolutes. Society's beneficence-based concerns must be expressed just at the point of denial of life-prolonging treatments to persons based on moral absolutism. A key ethical category here is the "separability" or "independence" of the morality of abortion from the morality of using the tissue for research.] (Human Fetal Transplantation Research Panel, vol. 1, 1990, question 1, pp. 1-2)

Case 2. A similar but less settled case: I. B. 2.

Deriving PSCs from excess embryos donated by couples in infertility treatment is permitted in the private sector but forbidden in the federal sector. However, the DHHS General Counsel's opinion permits NIH to fund research "downstream" from PSC derivation supported by private funds. [Note: NIH has received letters signed by 70 members of the House and 5 Senators who challenge the legal opinion of DHHS General Counsel.]

Cases 1 and 2 are morally similar in concerns based in beneficence and respect for autonomy. Society and science both benefit in many ways by permitting research with excess embryos. To derive PSCs from blastocysts for research only adds to the benefits of this research activity. The principle is consistent with Case 1: although morally controversial with some, society ought not to forgo these opportunities for benefits. Embryo donation for research is already widely practiced in infertility clinics and in the private sector.

Cases 1 and 2 are also similar in autonomy-based obligations to respect parental choices to donate excess embryos for research and the procreative motives from which the original decision was made to generate embryos by IVF. Couples donate these embryos to help others and improve science. Embryos are created by couples who care for them and want to reproduce themselves. These embryos are within a web of caring relationships and not isolated "research material."

Cases 1 and 2 are morally different in one important respect: the fetus as a source is dead (although its cells are alive) and cannot be harmed by the research activities; the donated embryo is living but will die in the process of research (although its PSC cells live on and will differentiate into other somatic cells). The research activities (and the researcher) cause the demise of the embryo, a very different feature of Case 2 than in Case 1. Contrasting perspectives on the moral status or standing of the human embryo are relevant just at this point.

One perspective holds that fetal tissue research is morally more problematic than donating embryos for research, based on the view that the loss of a fetus, even at 8-9 weeks of gestation, occurs in a context of greater value (to the parents and society) than loss of an preimplantation embryo. This perspective views abortion is a more serious moral issue than selection among 3-4 embryos for possible implantation or research. Another moral perspetive, grounded in a belief that protected human life begins at fertilization, would view both losses as equivalent in human value to the loss of a person or potential person. These losses would, in this view, be moral crimes. Yet a third view, would see these acts as either morally neutral or involving no loss at all worth regarding in the moral realm. (Note: the NBAC cannot avoid taking a position on the moral status of the embryo if it focuses on Case 2)

The moral principle that has guided a number of official bodies (Ethics Advisory Board, Human Embryo Research Panel, and others) in justifying embryo research is that while respect for its human orgins and potential is due to the embryo, the degree of respect due is not equivalent to that due to persons. This is a principle of "qualified respect." A perspective developed along these lines by the Embryo Panel was criticized by Annas, Caplan, and Elias who stressed that an embryo's moral standing is not only due to a "cluster of properties" that it possesses but also from the "interests that potential parents and society bring to procreation and reproduction.." (p. 1131) [There is an opportunity here to amplify the arguments offered by the Embryo Panel and to make them more persuasive.]

Concerns based in nonmaleficence: the Human Embryo Research Panel carefully outlined a set of principles and guidelines (1994, vol 1, pp. x-xi) to prevent abuses and minimize harms to societal values and human beings. In brief, these were: 1) scientific competence of investigators, 2) valid research design and scientific/clinical benefits, 3) research cannot be otherwise accomplished (prior animal research required), 4) restricting number of embryos required for research, 5) informed consent of embryo donors for the specific research to be undertaken, 6) no purchase or sale of embryos for research, 7) IRB review, 7) equitable selection of embryos, 8) 14-day limit on length of research.

[Note: The issue of access to an adequate "supply" of PSCs for research is related to the source issue. Hogan argues, p. 3 that cell lines from several different sources should be available for research. She thinks it unwise to rely entirely on PSCs derived from fetal germinal cells; she cites methylation issues. Also, the federal ban that prevents the NIH from funding Thomson's work in deriving PSCs from excess embryos, if continued, would give Univ.

Wisconsin-Geron a virtual monopoly on access to these cells. Although the patent on the method and the cell is a fact, it would promote competition among laboratories if the NIH could fund other approaches to deriving PSCs from blastocysts. Hogan also makes a point of respect for the altruism of the donors.]

Case 3. I. B. 3. PSCs to be derived from human (or hybrid) embryos generated asexually by somatic cell nuclear transfer (SCNT), using enucleated human or animal ova for fusion.

Virtually nothing is known scientifically about SCNT as a source of human PSCs, unlike Cases 1 and 2. Case 3 is ranked above Case 4 due to the therapeutic potential of autologous PSCs -- to grow cells to return to the patient, in theory without graft vs. host rejection problems. When one considers the prospective clinical benefits of SCNT-created PSCs, it seems intuitively that there would be more moral support for Case 3 than for Case 4. A balancing and controversial factor is that the product of SCNT (using an enucleated human egg) is clearly a human embryo which could become a human being if transferred to a uterus. The NBAC's recommendations for a ban (with sunset provision) on cloning a human being are relevant here. Clearly, SCNT as a source of PSCs could not be pursued without a clear ban on making a baby by this method.

Case 3 is arguably different from all other cases due to the asexual origin of the source of PSCs, although donation is involved. In Case 3, individuals donate a somatic cell and an ovum for asexual reproduction of the DNA in the nucleus of the somatic cell. Are embryos from this source of less moral worth than sexually generated embryos? The answer is related in part to intent: creating embryos by SCNT would be done to promote clinically promising research to help human beings, which is a very different case from the original intent with which embryos in Case 2 were made, i.e., procreation. However, if one would not argue that embryos deliberately created for research (Case 4) are of less moral worth than "excess" embryos, then the embryos in Case 3 should not be so viewed. An embryo is an embryo, however made. However, to go throughly down the SCNT road requires a full scale review on its own and probably more time than NBAC desires to allocate to this topic.

Considering intent, Case 3 is more similar to Case 4, i.e., creating embryos for the sake of research, than it is to Cases 1 and 2. Considered consequentially, Case 3 is similar to Case 2 and 4, since embryos for research are the result.

Case 4. I. B. 4. PSCs to be derived from human "research" embryos created from donor gametes for the sole purpose of deriving PSCs for research

Although the result is the same -- research involving human embryos -- Case 4 involves an important and morally relevant difference from Cases 1 and 2, i.e., the deliberate creation of embryos for research from donated gametes. The donors may be individuals or couples, depending upon the circumstances. Whether one views this activity as a major step in moral evolution that is justifiable for compelling scientific and clinical reasons (as I do) or as laden with "symbolism" (Robertson), there are reasons to argue that Case 4 is different and more complex morally than Cases 1 and 2. One reason is that creating embryos for PSC research is a precedent to recruit embryos for germline gene transfer research from couples at high risk for genetic disease. Does the NBAC have the time and resources to conduct a thorough review of germline gene transfer? Other groups (AAAS Taskforce and RAC) are reviewing intentional and unintentional germline gene transfer.

Is an adequate supply of PSCs for research relevant in this case? Will scientists really need the option of I. B. 4. for an adequate supply? Possibly a "wait and see" position is the best response here. This writer (with Peter Waldron, M.D.) prepared a paper in 1993 for for the Human Embryo Panel arguing that recruiting gametes for embryo research was necessary to understand gene expression or genomic imprinting in the embryo to inform attempts to alter mutations. However, such preparatory work in pathophysiology may not be necessary if success is achieved in the laboratory in genetic alteration of cells, including PSC-assisted gene therapy. The scientific need for I. B. 4. is still debatable, in my view. [My latest information about the U.K. is that this option is infrequently used, although permitted by law, and excess embryos are most frequently used for embryo research; Jayne Spink.]

In addition to their major arguments in support of Federal funding of this option, the Human Embryo Panel justified Federal funding (subject to additional review) of this activity to generate PSCs for research. There was a debate among panelists about the moral and scientific justification of this recommendation. The issue concerned creating banks of cell lines from different genotypes that encoded different transplantation antigens, the better to respond to the transplant needs of different ethnic groups. This would require recruitment of embryos from ethnically different donors. However, the possibility of genetic alteration of genes controlling the major histocompatibility complex would obviate this step. This is a scientific question that still remains unanswered today (Gearhart, Science 6 Nov 1998, 1061).

In addition to important differences between Cases 1-2 and 3-4, a review of the scientific background and need for research in Cases 3-4 would be a major undertaking which could not be completed in the time frame proposed by NBAC. In summary, an incremental approach to these cases seems to indicate that NBAC should concentrate on Cases 1-2 and include some attention to Cases 3-4

with emphasis on the similarities (these yield PSCs for research) and major differences as to means and ends.

Weaknesses of an incremental approach: Those who hold the strongest views on the morality of fetal and embryo research would likely be critical of an incremental approach as violating their basic ethical principles. On the one hand, some (Harris, 1992) argue that if it is right to use embryos for research, it is right to create them for this purpose, especially for answers that cannot be obtained otherwise. This view would see an incremental approach as timid and evasive of the real issue -- embryo research -- and giving away too much to conservative views. On the other hand, those who argue that human embryos and fetuses ought to be protected by society from destruction (for any reason) because of their existing or potential equality with other human beings would not concede that any of the cases (1-4) are morally acceptable. This view would see the incremental approach as fatally compromised by adopting the wong first premise, namely, the acceptability of research with PSCs derived from human fetuses following abortion. The NBAC should expect criticism from adopting an incremental approach from both of these sources.

IV. Public Policy: Should the Ban be Partially Lifted?

NBAC should weigh the effect of the ban on embryo research on PSC and other valuable research. One effect is to give Geron-related labs a monopoly on I. B. 2. as a source of PSCs for research. Is it in the public interest to promote this monopoly of access? Even if the ban were lifted, Geron has a patent on the approach and the "cell" and would profit from any discoveries made from this approach. However, a partial lifting of the ban would enable the NIH to fund approaches to deriving embryos from blastocysts as well as involve its own intramural research program in this arena.

Lifting the ban to permit federal funding of research with excess embryos would bring the NIH into the PSC research arena both extramurally and intramurally. This result would predictably improve the scientific quality of the process prior to clinical trials of cell-directed therapy. It could also shorten the hiatus between basic research and therapeutic results. Meanwhile, the NIH's research mission in embryology, infertility, and genetic disease has also been seriously hampered by the embryo research ban. The ban and fear of Congressional punishment of even the appearance of NIH encouragement of any embryo research has had a chilling effect as intended. For example, the NIH "ad hoc" review panel recommended by the Human Embryo Research Panel (vol. 1, p. 73) was never appointed. The lack of a review mechanism for such research has been a discouragement to proposals, even if their methods were not proscribed by the ban. The NIH Director has stated that a panel will be created to guide NIH decisions to fund PSC

research. However, the needs to be met by embryo research are much wider than PSC research. This section concludes with the Embryo Panel's list of research activities that could be conducted with donated excess embryos.

- improving clinical protocols used in IVF programs for the treatment of male and female infertility;

- improving techniques for preimplantation diagnosis of genetic and chromosomal abnormalities;

- providing high-quality information about the morphology, biochemical and biophysical properties, genetic expression, and similar characteristics of pregastrulation stage human embryos;

- enhancing knowledge of the process of fertilization;

- facilitating the design of new contraceptives;

- studies of teratology and the origins of certain birth defects;

- increasing knowledge about cancer and metastasis, including the causes of certain reproductive cancers;

Partial lifting of the ban would lead to correction of a longstanding and unfair barrier to the NIH's full role in research to gain knowledge on these vital questions. Closing the gap between diagnosis and therapy in the Human Genome Project is also relevant here. However, current federal science policy on genetics and embryo research presents a basic moral and political contradition. One the one hand, Congress is liberally funding the Human Genome Project that is multiplying diagnoses of mutations that cause untreatable genetic diseases or heighten the risks for cancers, heart disease, diabetes, and stroke. At best, there are only "halfway therapies" for most of these common diseases. On the other hand, the embryo research ban blocks a promising and current way for the whole nation to share the benefits and burdens of learning whether the huge gap between diagnosis and treatment can be narrowed. Is it fair to taxpayers to fund gene diagnosis and continue to ban federal support to learn how to achieve cell-directed therapy by deriving PSCs from blastocysts of donated embryos?

My view is that using donated excess embryos for PSC research has as much moral and public policy acceptance as does research with fetal tissue. The main reason is the origin of the embryos occurs with parental intent of procreation. There are several supporting facts for this view. The Human Embryo Research Panel recommended this option as acceptable for federal funding without

"additional review." (1990) President Clinton was on record at the time as accepting this option; there was a tie vote (26-26) in the House Appropriations Committee (July, 1995) on an amendment to permit federal funding for this option; and see Annas/Caplan/Elias article (NEJM, 5/16/96) for more arguments, namely that excess embryos do not have a "manufactured orphan" status. (1331)

Recommendations to the NBAC:

1. In addition to a review of what the DHHS legal opinion permits (Case 1 + research "downstream" from derivation of PSCs from blastocysts), NBAC's report in response to the President's request should focus most heavily on ethical issues of PSC research with "excess embryos" (Case 2). The scientific background for PSC research in Cases 3 and 4 is too meager at this point to inform a truly "thorough" review. NBAC can choose to defer review of Cases 3 and 4 to a later time in its own work or to outline the tasks to be done by other bodies.

2. The NBAC should explore taking a position favoring a partial lifting of the ban to permit Federal funding of derivation of PSCs from donated embryos as well as other long-standing and delayed Federally supported research activities in basic embryology, genetic diseases, and infertility research.