DRAFT #2

DELIBERATING INCREMENTALLY ON HUMAN PLURIPOTENTIAL STEM CELL RESEARCH

by

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I. INTRODUCTION [1]

The National Bioethics Advisory Commission (NBAC) faces major choices about the scope of its deliberations on ethical and public policy issues of human pluripotential stem cell (PSC) research. President Clinton requested that NBAC's "thorough" review include implications of a reported attempt to fuse a human cell with a cow egg.[2] With a June 1 goal for a draft report, "How thorough is thorough?" becomes a fitting question.

Part II of the paper describes three moral problems or concerns in PSC research and explores the scope of a full review of the issues. Part III discusses an alternative to an exhaustive review, i.e., an incremental or case-by-case approach. The strengths and weaknesses of this approach will be weighed. The paper concludes with recommendations drawn from the discussion, which includes a section on harmful effects of a total ban on federal support of embryo research.

Part III begins with NBAC's main tasks in relation to PSC research. Other national commissions and expert panels on fetal [3]

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[1] The author wishes to thank and acknowledge the help of Franklin G. Miller, Ph.D. and Kathi Hanna, Ph.D., with various sections of this paper.

[2] Wade, N. (1998). Researchers claim embryonic cell mix of human and cow. New York Times, Nov. 12, p. A-1.

[3] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Report and Recommendations: Research on the Fetus, 1975, U.S. Dept. of Health, Education, and Welfare (DHEW Publication No. (OS) 76-127). See also: Association of American Medical Colleges, Summary. Fetal Research and Fetal Tissue Research. June, 1988,

and embryo [4] research compiled an impressive record. NBAC can build upon this record in a new scientific context of stem cell biology and somatic cell nuclear transfer (SCNT) technology.

A. Public Bioethics and Incommensurate Moral Views

The central controversy in PSC research arises from differing moral approaches to the social practice of elective abortion or of using live embryos in research. An approach that concludes with moral condemnation of embryo research holds that it is a form of unjustified killing, because a living human embryo is a organism with genetic potential to become a person. In this view, research activities that would destroy that organism are morally unacceptable regardless of the good consequences desired.

An opposing approach not only permits preimplantation embryro research to increase benefits to science, society, and patients, but holds that the practice raises no substantive ethical questions. For this approach, without implantation and gestation to fetal viability there is not a person with interests to protect. These opposing positions make incommensurate evaluations of the moral status of human embryos. They may also

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and National Institutes of Health, Report of the Human Fetal Tissue Transplantation Research Panel, vol. 1, December 1988.

[4] Ethics Advisory Board, U.S. Dept. of Health, Education, and Welfare, Report and Conclusions: Support of Research Involving Human In Vitro Fertilization and Embryo Transfer, (Washington, DC, US Government Printing Office, 1979); National Institutes of Health, Report of the Human Embryo Research Panel, vol. 1, Sept.

have dissimilar worldviews and basic moral perspective.

To date, NBAC's discussions largely reflect a third approach, which recognizes important moral concerns within each opposing position. This approach cannot find consensus on the foundations of moral norms to guide embryo research, but it can seek moral consensus on cases, mid-level principles, and safeguards. As a public bioethics body, NBAC should be satisfied to reach consensus on what it would permit, forbid, or defer regarding PSC research. That consensus ought to be informed by history, international experience, and the best moral lights of the commissioners. Neither society nor a public bioethics body can reconcile the differences between opposing evaluations of the moral status of the embryo. NBAC and society can gratefully recognize that in a democracy the several states can choose to embody varying views of the moral status of embryos in their laws. So does democracy function to ameliorate the divisiveness of irreconcilable moral views.

The ethics of embryo research is a very recent controversy. Until recent times, procreation was the only morally acceptable reason to create an embryo. To view research with embryos as also morally acceptable is a relatively novel moral belief.[5] The

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1994.

[5] President Clinton's own response to the Embryo Panel's recommendations in 1994 illustrate this point. He could accept research with excess embryos but not with embryos created only for research. Marshall, E. (1994). Human embryo research. Clinton

evolution of moral beliefs guiding social practices and institutions occurs very slowly. Conflicts of loyalties and intense struggle -- not always peaceful -- mark the path of such changes.[6] In open and democratic societies, the electorate -- informed by voices of contending moral traditions -- must participate to guide the scope and pace of moral evolution. National and state commissions in bioethics play a key role in this process in open democracies.[7] NBAC's work on these issues will predictably play a role in the moral policy that will be embedded in state laws on embryo research.

II. Human PSC Research: Clinical Promise and Moral Concerns

A. Human PSC Research

The clinical promise of human PSC research is cell-replacement therapy for disorders caused by early cell death or injury. [8] Scientists envision effective treatment for the most

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rules out some studies. Science, 266, 1634-35. An editorial, "Embryo research: drawing the line," Washington Post, Oct. 2, p. A21, 1994 had earlier expressed the same view.

[6] An excellent discussion of the slow pace of cultural change in the context of the moral implications of Darwin's discovery of evolution by natural selection, is Rachaels, J. (1990). Created From Animals, (New York, Oxford University Press).

[7] Fletcher JC, Miller FG (1996). The promise and perils of public bioethics. In The Ethics of Research Involving Human Subjects: Facing the 21st Century, H.Y. Vanderpool, ed. (University Publishing Group, Frederick, MD, 1996), pp. 155-184.

[8] The best single summary of the clinical potential of human PSCs derived from germinal fetal tissue and blastocysts of human embryos is Gearhart, J., (1998), New potential for human embryonic stem cells. Science, 282, 1061-62.

common diseases, e.g., leukemia, diabetes, Alzheimer's disease, liver and heart disease, injuries to the spinal cord, and many more. PSC research is only one of several dramatic advances in stem cell biology [9] that promise gradually to replace many of the "half-way" therapies (e.g., hemodialysis, organ transplants, chemotherapy, enzyme replacement, etc.) that are now the standard of care.[10] Thirty-three Nobel laureates' letter recently expressed these hopes to the President and members of Congress.[11] The scientific imperative now points beyond successes in

[9] E.g., see reports on how cells within the ependymal lining of the adult mouse brain ventricles may be multipotent neural stem cells (NSCs) capable of generating new neurons and glia (Johansson, C.B., et al. Cell 96, 25-34, 1999) and how similar cells can regenerate blood tissues when transplanted into an irradiated mouse (Bjornson, C.R., et al. Science 283, 534-37, 1999). Bjorklund and Svendsen reviewed this work (Nature 397, 569-70, Feb. 18, 1999) and commented: "We do not know whether human neural cells also arise from the ependymal layer, or whether they have the capacity to turn into blood. However similar embryonic human cells can be cloned (Flax, J.D. et al. Nature Biotechnol 16, 1033-1039, 1998), grown for extended periods (Svendsen, C.N., et al. J. Neurosci Methods 85, 141-52, 1998) and continue to reside in the adult brain (Eriksson, P.S., et al. Nature Med 4, 1313-1317, 1998), so it may not be long before we find out."

[10] These advances promote some of the most remarkable hopes (both of cures and profits). An example is William Haseltine, CEO of Human Genome Sciences, Inc., who predicts that today's leading killers - heart disease, cancer, Alzheimer's disease, and the "aging process itself" will gradually become distant memories. He predicts that a century from now, "death will come mainly from accidents, murder, or war." Ignatius, D., (1999). The revolution within. Washington Post, March 8, A-19.

[11] American Society for Cell Biology, Letter to the President and Members of Congress, March 4, 1999. Citing a large body of successful work with mouse PSCs, the letter states that PSC research has "enormous potential for the effective treatment of human disease," and argues that the President and Congress should

research with mouse models and higher animals, e.g. Thomson's work on PSCs derived from embryos of marmoset monkeys, [12] to novel experiments with human PSCs.

B. Moral Problems of PSC Research

Alongside these hopes, difficult moral and public policy concerns confront scientists, policy makers, and the public. PSC research raises three specific moral problems. The first is about the moral legitimacy of access to each source of PSCs.

1. Access to Sources of PSCs.

Table 1 ranks the sources of PSCs by degree --in my view-- of moral and legal acceptability of access and of moral controversy. The discussion refers to these sources as "Cases" 1, 2, 3, and 4.

Table 1. Sources For Deriving PSCs

1. PSCs derived from human fetal tissue[13] following elective abortion (e.g., Gearhart research).

2. PSCs derived from human embryos available in excess of clinical needs to treat infertility by in vitro fertilization (IVF); with informed consent, parents donate excess embryos for research (e.g., Thomson research).[14]

3. PSCs to be derived from human (or hybrid) embryos

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permit federally funded researchers to work with PSCs.

[12] Thomson, J.A. et al. (1995), Proc Natl Acad Sci USA 92, 7844.

[13] Shamblott, M.J., Axelman, J., Wang S., et. al. (1998). Derivation of pluripotent stem cells from cultured human primordial germ cells. Proc Nat Acad Sci USA, 95, 13726-13731.

[14] Thomson, J.A., Itskovitz-Edor, J., Shapiro, S.S., et al. (1998). Embryonic stem cell lines derive from human blastocysts. Science, 282, 1145-1147.

generated asexually by SCNT (using enucleated human or animal ova).[15]

4. PSCs to be derived from human embryos created, with informed consent, from donated gametes for the sole purpose of research.[16]

Part III of the paper explores an incremental approach to the ethical issues raised by access to these sources. NBAC can note at the outset, however, that a reformed federal science policy would not require funding access to all sources of PSCs at once. It is now illegal for federal agencies to fund any work that requires access to embryos with any other intent than therapeutic.[17] An important change in this policy is underway with significant support in Congress. Described more fully below, the National Institutes of Health (NIH) has been legally advised that the agency can fund some research with PSCs derived

[15] Has this been done in the mouse? A report has cast serious doubt on claims of Korean researchers to have cloned a human embryo by transferring the nucleus of a somatic cell into an enucleated egg cell, both from the same patient. Baker, M. (1999), Science, 283, 617-18. A U.S. biotechnology company also disclosed a 3 year old experiment (but no scientific report) fusing an encucleated cow's egg with a human cell. Wade, N. (1998, November 12). New York Times, p. A-1.

[16] Research embryos are created by infertility researchers in the private sector in the U.S., and law in the U.K. permits the creation of research embryos under strict control. No research with PSCs has been reported with "research" embryos as the source.

[17] In my view, to conduct "therapeutic" research with embryos without a foundation of prior knowledge gained through investigative research into pathophysiological and genetic questions would be totally irresponsible. A solid pre-clinical basis must be laid for any new stage of therapy. Nonetheless, it is legal under the federal embryo ban to attempt therapeutic experiments.

by private funds but not activities that access (and destroy) embryos at the blastocyst stage. If a) Congress permits this legal interpretation, b) the NIH oversees and guides the new step successfully, and c) important new and clinically relevant information results from NIH funding, the public policy stage may be more open to a review of the existing ban. For reasons given in Part III, there can be support to modify the ban in due time to permit federal support for access to embryos in Case 2. The issues about federal funding for access to embryos in Cases 3 and 4 are more complex than Case 2, as the discussion will show. In Case 3, it remains to be determined whether human embryos can be created by SCNT and whether these embryos will be biologically identical or different from those in Cases 2 and 4. The arguments for federal funding to access to embryos in Case 4 are stronger today than in 1994 because of PSC research, but the deliberate creation of embryos for research with federal funds remains controversial enough to overwhelm debate about federal policy to permit Case 2. Phased access to embryos in the federal sector of science is a concept that parallels an incremental approach to review of the four sources of PSCs.

2. Can Access Be Separated from Uses?

A premise of this paper is that NBAC must address moral issues of access to embryos prior to issues about uses. Before the section on uses, this question about "separability" of these

issues can be examined. Federal law does not prohibit embryo research in the private sector. It is now legal, except in states that prohibit it, [18] to expose live embryos to research. From a premise of the legality of abortion, the Human Fetal Tissue Transplantation Research Panel [19] argued that it could separate its deliberations on the morality of the uses of fetal tissue from the morality of abortion and took no explicit position on the latter. In theory, NBAC could take the same approach.

This approach has appeal, but there are reasons for NBAC to be less confident than the Fetal Tissue Panel was about using it. The first stems from the relationship of law and morality. Law does express moral beliefs and values; the law can rightly be seen as a floor for morally permissible acts. But there are stronger and weaker floors. The point is that absence of law is a weaker argument for moral acceptability than positive law that bars unwarranted intrusions into a lawful choice, such as

[18] Louisiana is the only state that expressly "forbids any person to destroy a viable embryo." Andrews, L. (1994). State regulation of embryo research. In National Institutes of Health, Papers Commissioned for the Human Embryo Research Panel, vol. 2, p. 299. However, the language of state laws in nine other states (Maine, Michigan, Minnesota, North Dakota, Pennsylvania, Rhode Islan, and Utah) that ban embryo research "would appear to prohibit the development of cell lines out of embryos, if the procedure is considered a research procedure, since it would not be seen as therapeutic or beneficial to the embryo." Andrews, p. 301.

[19] See footnote 11, Human Fetal Transplantation Research Panel (1990) vol. 1, question 1, pp. 1-2.

elective abortion. Far greater quantity and quality of moral experience and ethical reflection (on both sides of the issues) has helped to shape U.S. abortion law than did shape the federal ban or influenced many states which do not prohibit embryo research. An argument that nonprohibition is a floor for moral acceptability of access to embryos for research is too weak to overcome an objection that the several states have not had the opportunity to hear both sides and legislate in the present context. Another objection will also be that NBAC avoided the moral debate of the access question but smuggled in a position underneath a shaky legal argument. Law does not prohibit many activities and choices that are open to serious moral challenge, such as sex selection by prenatal diagnosis. For this reason, there is a need for a fuller moral defense of access to live donated embryos for research than one afforded by an absence of law.

The second reason is the need for a contemporary moral analysis of embryo research that accounts for criticisms of the moral perspective offered by the Human Embryo Panel and which is informed by the present state of science and public policy. Whether the NBAC can come to consensus on the access question must be explored. Whatever the outcome, the NBAC can then assess the public policy and political context within which to make its recommendations.

2. Uses of PSCs in Research in Relation to Access

The second moral problem concerns uses of PSCs in research. Are all present and prospective uses of PSCs for research morally acceptable? Are all such uses acceptable for federal funding? These questions are also relevant to choices about the total scope of NBAC's deliberations.

Dr. Varmus [20] and others describe three general areas of research uses of PSCs: 1) learning how PSCs develop and differentiate into specific types of cells, 2) studying toxicity and beneficial effects in the context of drug development, and 3) growing cells of different types for transplants to repair or replace patients' injured or dying cells. Dr. Thomson [21] and Dr. Varmus caution that it will take as long as five years to lay foundations for testing cell replacement therapies in humans. Whatever the time required, support from the NIH and the National Science Foundation (NSF) will mean more rapid progress to therapeutic trials.

Questions of scientific merit, utility, and linkage to larger disputes can be raised about uses of embryos in research. Assuming that no overriding moral reasons call for society to forgo completely the benefits of access to embryos, the moral

[20] Varmus, H. (1999). Testimony before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies. Jan. 26, p. 3.

[21] Smaglik, P. (1998). Stem cell scientists caution: clinical applications remain years away. The Scientist, 12, 1,6, Nov. 23.

considerations about uses ought to focus first on issues of scientific justification and utility and secondly on linkage to unresolved and controversial uses. If embryos are to be used in research, the scientific reasons need to be coherent and defensible in peer and IRB review processes. The number of embryos needed for experimentation is related to an obligation to use the minimal number required to gain the desired knowledge. This issue is also related to an issue of supply of embryos for research, which is shaped by practices in infertility treatment centers and the percentage of IVF embryos that will be eventually discarded. Part II gives some preliminary information on this situation which requires more research but raises concern.

Thirdly, some proposed uses of PSCs are linked to large and unresolved controversies still facing society and policy makers. For example, in reviewing Cases 3 and 4, NBAC must also choose whether it will fully revisit the debates about human cloning and human germline gene transfer.

Uses: Immediate, Possible, and Controversial. Scientists agree that the most immediate uses of PSCs are in studies of cell differentiation and differences between properties of PSCs derived from fetal tissue (Case 1) and donated embryos (Case 2) and between cell lines grown from these two sources. Dr. Brigid Hogan [22] noted differences in DNA between cells derived from

[22] Hogan, B.L.M. (1999). Statement to NBAC. Feb. 3, p. 3.

embryonic "germ" (EGs) and embryonic stem cells (ESs). The differences may be due to methylation, a process that protects recognition sites of DNA and plays a regulatory role in gene expression. Cells derived from EGs may have less methylation than normal. The scientific and clinical import of these differences needs exploration and raises no special moral concerns. Dr. Hogan stressed the necessity of access to both types of cells for this purpose.

Dr. Gearhart [23] outlined other straightforward and morally unproblematic questions about PSCs derived from excess embryos (Case 2): i.e., about ways to assay blastocysts for their potential of yielding PSCs (perhaps by searching for genes that predispose for this capacity), to produce more cell lines than the five grown by Thomson's work, as well as other intrinsic or extrinsic factors that foster success. Presumably, using PSCs and cell lines in research on drug development will build upon prior research on differentiation and knowledge about cell lines grown from PSCs from various sources.

Eventually, PSCs isolated from SCNT-generated human embryos (Case 3) will be needed to study differences, if any, between cell lines grown from PSCs derived in the contexts of Cases 1 and 2. Also, embryos produced by cloning technology, using the somatic cells of patients, will be needed to study the

[23] at note 1, 1062.

feasibility of autologous cell replacement therapy and avoid the graft-vs.-host reaction. A question about lesser moral worth of SCNT-generated embryos has surfaced in NBAC discussion[24] and needs careful reflection related to scientific information not now available.

Research embryos (Case 4) as a source of PSCs will be needed to create banks of multiple cell lines representing a spectrum of alleles for the major histocompatility complex. This goal requires that ova and sperm of persons with specific genotypes be selected to create embryos from which to derive particular PSCs. This use falls into the category of Case 4, a similar activity to studies of embryonic gene expression in a particular disease.[25] Infertility centers, using private funds, now create

[24] National Bioethics Advisory Commission, 26th Meeting, January 19, 1999, pp. 16-17.

[25] A paper was prepared for the Human Embryo Research Panel on the case for recruiting embryos from couples whose children were at risk for cancers caused by genomic imprinting, in order to study this disease process: Fletcher, J.C., Waldron, P., "Childhood Cancers and Human Embryo Research," April, 1994. The Panel's report cites the paper, vol. 1, with a notation that the arguments in the paper "are open to debate and not accepted by all experts." Current research on genomic imprinting assists counseling and prenatal diagnosis, e.g., Buiting, K., et al., (1998). Sporadic impriting defects in Prader-Willi syndrome and Angelman syndrome: implications for imprint-switch models, genetic counseling, and prenatal diagnosis. Am J Hum Genet 63, 170-80. Our point in 1994 was that understanding of genomic imprinting in the embryo could be useful in diagnosis and treatment of these diseases in children. An example of the study of gene expression in the embryo is Bondurand, N., et al. (1998). Expression of the SOX10 gene during human development. FEBS Letters 432, 168-72, Aug. 7. This gene is the key factor in Shah-Waardenburg syndrome.

embryos to study the viability of frozen ova or to improve the medium in which embryos grow after IVF. This work is regulated only by the ethics of professionals, a porous protection at best in the present marketplace of medicine. Shaping a unified policy and regulatory oversight for U.S. embryo and fetal research is a long-term and challenging task. This task has affinity with the challenge to unify regulation and oversight of practices in research with human subjects in the private and public realms.

This section on uses concludes with the potential for PSCs in research on human gene therapy. PSC-assisted gene therapy may resolve major technical problems in using exogenous vectors to transport corrective DNA to target sites. Dr. Austin Smith's testimony to NBAC pointed to this use [26] as did a NIH discussion paper on cloning.[27] In the context of somatic cell gene therapy, the use of PSCs raises no new ethical questions. Dr. Erik Parens' testimony to NBAC noted how PSC research will converge into gene transfer experiments in the germ-line of human embryos for therapeutic reasons.[28] A truly "thorough" and far-ranging review of PSC research would examine the scientific and ethical issues in this topic.

In summary, the most immediate uses of PSCs in research are

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[26] Smith, A., Testimony to NBAC, Jan. 19, 1999, p. 36.

[27] National Institutes of Health, (1998). Cloning. Present uses and promises. April 27. (Available from the Office of Science Policy)

[28] Parens, E., Testimony to NBAC, Jan. 19, 1999, p. 98.

consequent to derivation from Cases 1 and 2. Future uses of PSCs derived from Cases 3 and 4 are related to the pace of scientific advances. If human embryos can be generated by SCNT, there will be a need to compare the properties of PSCs derived as in Case 3 with PSCs from other sources. Any future guidelines about deriving PSCs from embryos in the context of Cases 3 and 4 would need safeguards on implanting a SCNT-created human embryo or using PSCs to assist in human germ-line gene transfer experiments. The Food and Drug Administration (FDA), advised by the NIH's Recombinant DNA Advisory Committee (RAC), has oversight and authority over any proposed germ-line interventions.

3. Effects of a Ban on Federally Funded Embryo Research

Congress bans federal support of any research "in which a human embryo.. [is] destroyed, discarded, or knowingly subjected to risk of injury greater than that allowed for research on fetuses in utero.."[29] The term "human embryo" in the statute is defined as "any organism.. that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells." The ban is transitory in the sense that it is revisited each year when the language of the NIH appropriations bill is considered.

The ban reflects a moral view that embryos deserve absolute protection from society because of their unique status and

[29] Pub. L. No. 105-78, 513(a) (1997).

potentiality. However, some effects of the embryo research ban raise serious moral and public policy concerns for those who hold opposing or moderate views of the ethics of embryo research.

First, the ban conflicts with several of the goals of medicine, especially healing, prevention, and research.[30] Beneficence impels the pursuit of each of these goals and undergirds moral obligations to prevent or ameliorate human suffering caused by disease. The moral traditions of biomedical research reflect such loyalities, tempered and balanced by commitments to "above all (or first) do no harm."[31] The question of whether harm can be done to preimplantation embryos in research is discussed in Part III. The NIH Human Embryo Panel's Report in 1994 [32] made a strong case for federal funding of embryo research to meet this obligation. The ban's most immediate moral effect is to infringe loyalty to these goals of

[30] Medicine is a goal oriented profession. Leon Kass argues that medicine has one absolute end: healing. (1985. Towards A More Natural Science. New York: Free Press.) His claim is overstated, because it is clearly problematic to fit other valid goals of medicine (e.g., prevention and research) under healing. Actual experience recommends viewing medicine as having multiple, complex, and sometimes competing goals: to save life and cure disease; to relieve pain, suffering, and disability; to rehabilitate and restore function; to prevent disease; to improve the quality of living and dying; and to seek new knowledge. This more complex view is reflected in Miller F.G., Brody, H. (1995). Professional integrity and physician-assisted death. Hastings Cent Rep 25, 8-17.

[31] Beauchamp, T.L., Childress, J.F. (1995). Principles of Biomedical Ethics. 4th edn. (New York, Oxford University Press), p. 189.

[32] See footnote 9.

medicine by preventing federal support for acts in research that harm or discard embryos.

A second effect is to encourage neglect of public policy on embryo research. A practice in the U.S. is to ameliorate some moral disputes -- especially about human reproduction -- by denying federal funding (e.g., elective abortion, embryo research) but not interfering with the activity in the private sector. The U.S. has a ban on federal funding but no public policy for embryo research. There is a widespread practice of unregulated investigative embryo research on the fringes of public life. At best, these activities are guided by traditions of self-regulation in science and medicine.

A third effect is to inhibit research needed for experimental treatment, which extends a older chilling effect on fetal research onto embryo research. The language of the embryo ban reflects older federal policy on fetal research. In 1985, Congress imposed sharp restrictions [33] on federal support for investigative fetal research, especially in context of abortion. No federal agency since has funded any investigative ("non-therapeutic") fetal research. The result is a dearth of information about normal fetal physiology and development required for sound fetal therapy experiments. For example,

[33] National Research Extension Act of 1985, P.L. 99-158, 99 Stat. 820.

ignorance about fetal immunocompetence was a prominent topic [34] in NIH-RAC discussion of Dr. French Anderson's proposal for an in utero gene therapy experiment for adenodeaminase (ADA) deficient severe combined immunodeficiency syndrome (SCIDS), a disorder that destroys an affected child's immune system. Moreover, a recent NIH-supported Gene Therapy Policy Conference examined the scientific and ethical basis for experimental in utero gene therapy. The Conference affirmed the ethical argument to prevent inevitable harm to the fetus and future child. However, it found inadequate scientific foundations to proceed with such experiments in the near future.[35] Federal policy on fetal research contributes to an acute knowledge deficit while the technical feasibility of ultrasound-guided fetal gene therapy steadily grows. [36] However, absent sound foundations any such experiment would be an unconscionable "shot in the dark." If the total embryo ban continues, it is predictable that important pre-clinical information necessary for experimental gene transfer to prevent disease in the embryo (permitted by the ban but not now by the NIH-RAC) would not be available.

The ban's effects also infringe on distributive justice by

[34] Remarks of Dr. Roberta Buckley. NIH Recombinant DNA Advisory Committee (RAC) Meeting, September 24-25, 1998, p. 4.

[35] National Institutes of Health, Gene Therapy Policy Conference. Prenatal gene transfer. Scientific, medical, and ethical issues. Jan. 7-8, 1998. (Report forthcoming)

[36] Schneider, H., Coutelle, C. (1999). In utero gene therapy: the case for. Nature Med, 5, 256-57.

limiting optimal NIH involvement in infertility, cancer, and genetic research. These lines of research were approved by the Human Embryo Research Panel.[37] To be just in research means to distribute the benefits and burdens of activities fairly over a whole population. A disproportionate share of burdens and risks of embryo research falls upon private infertility patients and the private sector. These risks are all the more concerning due to lack of public oversight and regulation of embryo research. Finally, the is disrespectful to parental donors of excess embryos, who are also taxpayers with a condition of infertility long neglected in federal science policy and oversight.[38]

First Steps of Change. Change is underway in federal science policy for the first time since the embryo ban. In December, 1998, Dr. Varmus requested a legal opinion as to whether the NIH could fund PSC research. Harriet S. Rabb, General Counsel, DHHS, ruled that the NIH could legally fund uses of PSC research but not activities deriving PSCs from embryos.[39] She based her opinion on a scientific definition of PSCs as neither a human "organism" as defined by the statute nor capable of developing

[37] See footnote 9, pp. 7-8.

[38] U.S. Congress, Office of Technology Assessment, Infertility: Medical and Social Choices, OTA-BA-358 (Washington, DC: U.S. Government Printing Office, May 1988); Blank, R.H., (1997). Assisted reproduction and reproductive rights: the case of in vitro fertilization. Pol & the Life Sci 16, 279-288.

[39] Memorandum. Harriet S. Rabb to Harold Varmus. Federal funding for research involving human pluripotential stem cells. Jan. 15, 1999.

into a human being. If PSCs are not embryos, she argued, then the statute does not prevent NIH funding PSC research "downstream" from derivation of PSCs that was privately funded. Since the ban on embryo research only follows the public dollar, there are no legal restrictions on private or university funding such work, if the equipment and laboratory facilities are not purchased or operated with federal funds. The opinion also affirmed that existing federal law [40] permits NIH support of derivation and use of PSCs from fetal tissue. Dr. Varmus has stated that the NIH will convene an advisory committee to develop guidelines for funding "downstream" PSC research and conducting studies of PSCs.

Subsequently, Secretary Shalala received two letters signed by seventy House members and five Senators. The signers implored her to correct the legal opinion and reverse Dr. Varmus' decision to fund PSC research. The House letter [41] argued that the Rabb opinion evaded the linkage to and complicity in prior destruction of embryos. It also advanced a key legal interpretation, i.e., that Congress intended the scope of its ban to bar any tax dollars being spent on research which "follows or depends on the destruction of or injury to a human embryo". The key sentence was: "in the embryonic stem cell research which NIH proposes to

[40] P.L. 103-43, June 10, 1993.
[41] Letter. From Jay Dickey, et al. to Donna Shalala, Feb. 11, 1999.

fund, the timing, method, and procedures for destroying the embryonic child would be determined solely by the federally funded researcher's need for usuable stem cells." This language repeats identical language in federal regulations[42] on fetal research and law [43] on fetal tissue transplant research. The opponents are attempting to frame access to embryos for research in the same legal and moral context as access to the living fetus in the context of abortion. A choice of words often reflects a moral choice. "Embryonic child" shows how the dispute is joined.

Secretary Shalala answered [44] that the legislative history showed that the ban does not prevent federal funding of research "preceding or following" banned research in which embryos would be discarded or harmed. Her position was: "Proceeding cautiously with research on existing pluripotential stem is both legal and appropriate." Congress' decision about "downstream" PSC research is relevant to the scope of NBAC's public policy recommendations.

Assuming that Congress allows the Rabb ruling to stand, NBAC will still need to evaluate the moral arguments for and against access to embryos for research and attempt to reach a consensus position. Two directly opposing views, expressed by the Embryo Panel's Report and the Congressional ban, now confront one another in the nation's life. NBAC can clarify the the moral

[42] 45 Code of Federal Regulations ¶46. 206 (3).
[43] Public Law 103-43, ¶112 (c) (4).
[44] Letter. From Donna Shalala to Jay Dickey, et al., Feb. 23,

concerns on both sides and searching for moral consensus on mid-level issues, especially about Case 2.

III. An Incremental Approach to the Tasks of the NBAC

A. The Tasks of NBAC

Table 2 shows NBAC's four tasks in regard to ethical and public policy issues in PSC research:

Table 2. NBAC's Tasks on PSC Research

1) to clarify the ethical considerations relevant to deriving and using PSCs in research. NBAC must choose whether to focus on derivation and use from each source or only on the sources which have been reported to date, i.e., Cases 1 and 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.

4) to educate the public on the nature, promise, and risks of PSC research.

A "thorough" review requires completing each task for each source and the uses of PSCs in all four cases. The review would include, per Parens' argument, how PSC research converges into the longstanding debate about human germline gene transfer.

Obviously, there are problems with a full review. Case 3 lacks scientific information. Other groups are concurrently

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examining intentional and unintentional germline gene tranfer.[45] This task cannot be done in the proposed time frame. An alternative approach may better fit the NBAC's tasks and timeline.

B. An Incremental Approach: Strength and Weakness

NBAC and the nation face a group of cases or situations in which PSCs can be derived and used in research. How should NBAC morally deliberate about these cases?

This part describes and explores an incremental or case-by-case approach to NBAC's tasks. A strength is that scientists, ethicists, and attorneys are familiar with this approach. When presented with several morally problematic cases which appear to be similar, one can proceed incrementally, or case-by-case. One does not begin from first principles and work down or across, but with the case asking "What is morally at stake here?" As one explores the circumstances of the case, the principles and moral rules associated with the case and discussed in the literature about the case can be discerned. Beginning with the most "settled" case (or in science the most proven experiment), one then works outward, case by case, to complete certain tasks in

[45] A Task Force of the American Association for the Advancement of Science (AAAS) is studying the ethical, legal, and social issues in intentional germ-line gene transfer; the NIH-RAC is presently examining unintentional germ-line effects of somatic cell gene therapy.

moral deliberation.[46] One task is to compare and contrast moral similarities and differences among the cases. One searches especially for dissimilarities so sharp as to conclude that a case differs in kind and type and does not belong to this "family" or that "line" of cases. One finally reaches the least settled and most problematic cases in a line or see such clear differences between cases as to branch out to create other lines.

Another task is to discern the moral judgment linked to the case, as well as the guiding principles for the judgment that can hold from this case to a similar case. In ethics, this approach is known as casuistical reasoning.[47] After considering the

[46] A discussion of the key elements in such an approach that focuses on clinical cases is in: Fletcher, J.C., Lombardo, P.A., Marshall, M.F., Miller, F.G. (1997). Introduction to Clinical Ethics. 2nd edn. (Frederick, MD: University Publishing Group), pp. 21-38. The approach of "clinical pragmatism" discussed here is a hybrid that combines elements within casuistry, the dialectical method of moral reasoning used by Beauchamp and Childress (see footnote 31), and virtue ethics. A strong feature of clinical pragmatism is that it will be concerned as much with the issues of "who decides?" and "how ought the decision to be carried out?" as with "what ought the decision to be?" These issues are also relevant to moral problems in public policy decisions.

[47] The renewal of casuistry in a historical perspective is best discussed by Jonsen, A.R., Toulmin, S. (1988). The Abuse of Casuistry: A History of Moral Reasoning. (Berkeley: University of California Press). For an evaluation of the contribution of casuistry to biomedical ethics, see Beauchamp and Childress, at footnote 31, pp. 95-100. A valuable text in "pluralistic casuistry" is Brody, B. (1988). Life and Death Decision Making. (New York: Oxford University Press). Brody uses a model of "conflicting appeals" with complex clinical cases to gain insight about how the case should be resolved. Also, for an expert philosophical evaluation of the case by case approach, see Arras, J.D., (1991). Getting down to cases. J Phil & Med, 16, 29-51.

weakness of the approach, the remainder of this part illustrates how it can be used with these cases.

Case-by-case moral deliberation invites criticism from those whose method of moral deliberation is based on "an adequate account of morality as a public system that applies to all rational persons." [48] A case-by-case approach is bound to be less certain about the right account of morality but more certain about moral fallibility than other approaches. The point is that modesty about the place of ethical theory or systematization invites criticism. Those with sharply divergent view on fetal and embryo research will also disagree with this approach. John Harris argues that the distinction between Case 2 and Case 4 based solely on intention (to procreate or to make embryos for research) is weak. He argues for an all or nothing position. "If it is right to use embryos for research it is right to create them for this purpose. And if it is not right to use them for research, then they should not be so used even if they are not deliberately created for this purpose." An incremental approach distinguishes between the degree of moral acceptability of Case 2 and Cases 3 and 4. Harris criticizes this interpretation as timid and evasive of the most important issue, i.e. "taking responsibility for what we knowingly and deliberately bring

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[48] Clouser, K.D., Gert, B. (1990). A critique of principlism. J Med & Phil, 15, 234.

about, not simply what we are hoping for.." [49]

The view that human embryos and fetuses ought to be protected absolutely by society from research because of existing or potential equality with other human beings will not concede that any of the four cases is morally acceptable to any degree. In this view, an incremental approach is fatally compromised because it accepts the wrong principles in Case 1, namely, that access to human fetuses following elective abortion is morally acceptable. NBAC should expect criticism from both positions if it takes an incremental approach.

B. Case-by-Case Approach with the Four Cases

Case 1. 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."[50] Deriving PSCs from fetal tissue after elective abortion is clearly the most settled case of the four before the NBAC.

Some basic moral principles and rules are embedded in Case 1 and in the law permitting fetal tissue transplant research:

a) Beneficence. Although open to moral challenge, a sufficient and continuing moral consensus has emerged that

[49] Harris, J. (1992). Wonderwoman and Superman. (New York: Oxford University Press), pp. 45-46.

[50] Subsequently embodied in the NIH Revitalization Act of

society ought not to forgo the biomedical knowledge and/or therapeutic benefits to persons of uses of transplants with fetal tissue obtained after legal elective abortions. A consequentialist argument heightens the the obligation of beneficence in Case 1. The consequences of forgoing benefits from using fetal tissue are bad, and the consequences of using it are almost always good for science and patients. Also, unless the tissue is used in research, it will otherwise be discarded. In view of this risk of lost opportunity, and since elective abortions that open access to fetal tissue are legal, no overriding reason compels society to forgo this opportunity to benefit science and suffering persons. If society had morally condemned the research uses of fetal tissue because it was derived from electively aborted fetuses, very different moral principles and rules would be embedded in Case 1. What actually occurred was a gradual ascendency of respect for moral concerns on both sides of the issue shaping the earlier debate. These balancing concerns became embedded in the law and led to the current public process of federal funding for fetal tissue transplant research.

b) Respect for autonomy. Although some contest it, there is a sufficient moral consensus that society ought to respect the autonomous choices to donate fetal tissue for research of women

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who have made legal abortion decisions. If women have a liberty right to make abortion choices, it follows that the self-determination or autonomy expressed in that right extends to the choice to donate fetal tissue for research. Does the opportunity to donate fetal tissue positively influence the decision for abortion? In the only empirical study to date, a small number of women said that they would be more likely to have an abortion if they could donate fetal tissue for transplants.[51] This important first study did not explore the mechanism of influence or prove that this result is generalizable to larger populations. The study ought to concern those who argued that the opportunity to donate would play no substantial role in the decisions of women about abortion. More social-psychological research is clearly needed.

c) Nonmaleficence. Moral opposition to fetal tissue transplant research influenced a moral consensus about safeguards to prevent widening or encouraging the social practice of abortion. To this end, these moral rules are required: the consent process about abortion decisions must precede and be conducted separately from the consent process to donation of

[51] Of 266 respondents 32 (12%) reproted that they would be more likely to have an abortion if they could donate tissue for fetal tissue transplantation. 178 (66.9%) stated that they would not be more likely to do so, and 56 (21.1%) were uncertain. Martin D.K., Maclean, H., Lowy, F.H., et al. (1995). Fetal tissue transplantation and abortion decisions: a survey of urban women. Canad Med Assoc 153, 545-52.

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.

NBAC's review of Case 1 needs to cover the report of the Human Fetal Tissue Transplantation Research Panel,[52] the history of the "indefinite" moratorium,[53] and the legislative history of the Research Freedom Act. Also important is the history of fetal tissue transplant research funding by the NIH for several years within the federal requirements and without without significant incident.[54]

These considerations of Case 1 are not beyond moral challenge by a view condemning most elective abortions as unfair to the fetus and claiming that researchers who use fetal tissue are morally complicit with killing fetuses in abortions. To defend Case 1 adequately, NBAC's report must critically review

[52] See footnote 11.

[53] Fletcher J.C. (1990). Fetal tissue transplantation research and Federal policy: a growing wall of separation. Fetal Diagnosis and Therapy, 5, 211-225.

[54] U.S. General Accounting Office, (1997). NIH-Funded Research: Therapeutic Human Fetal Tissue Transplantation Projects Meet Federal Requirements. Report to the Chairmen and Ranking Minority Members, Committee on Labor and Human Resources, U.S. Senate, and Committee on Commerce, House of Representatives. US-GAO, Washington, DC, March.

the literature in the 1990s on the complicity issue.

Case 2. Case 2 is similar to Case 1 in three morally important ways. It is different in one clear and distinguishing feature. At the outset, one must concede that Case 2 is more controversial than Case 1 because it involves use of living embryos in research, although the term "embryos" must be further specified to the preimplantation stage, and further, that their use by researchers will not, under any circumstances, include human reproduction.

a) Beneficence-based considerations. First, similarly to Case 1, society and science can benefit in many ways by permitting research with excess embryos, as the Human Embryo Panel showed in 1994. Deriving PSCs from blastocysts and studying their potential can only add to these benefits.[55] Given research findings in the mouse, it appears likely that human beings will receive benefits from PSC research.[56] The NIH Embryo Panel supported federal funding of derivation of PSCs from embryos in 1994. Today, science and society are in much more verifiable proximity to this goal. Advances in PSC research,

[55] In the unlikely event that research proves that PSC research will not lead to cell-replacement therapy, science and society will be better off. A negative finding benefits science and prevents harmful experimentation.

[56] Rathjen, P.D., Lake, J., Whyatt, L.M., et al. (1998). Properties and uses of embryonic stem cells: prospects for applications to human biology and gene therapy. Reprod, Fertil, & Devel, 10, 31-47.

stem cell biology, and cloning technology are the major new factors in the scientific context.

lack of evidence that embryo research would yield clinical benefits was among several criticisms of the NIH Embryo Panel's position. Daniel Callahan [57] wrote that the Panel had not "cited a single actual benefit" from embryo research permitted in other nations or under private auspices in the U.S. Speculating that either there were no benefits to report or the Panel "just forgot to ask," he skeptically continued, "In any case we are asked to bet on the future benefits. I wonder what odds the bookies in Las Vegas would give on this one." Whatever the odds may have been in 1995, recent PSC research dramatically increase the odds that using human embryos as a source of PSCs will lead to major scientific and clinical benefits. PSC research adds strength to the consequentialist arguments that promote the obligations of beneficence in Case 2.

Secondly, Case 1 and Case 2 are similar with respect to the issue of discard. Whereas all fetal tissue is discarded if not made available for research, only a certain percentage of embryos will be eventually discarded.[58] The options for couples in IVF

[57] Callahan, D. (1995, Jan-Feb). The puzzle of profound respect. Hastings Cent Rep, 25, 39-43

[58] Reseach to date by the NBAC staff on the question of "discard" shows: 1) a wide variation of practices regarding consent for cryopreservation of excess embryos and choices about disposition of embryos, 2) only 10-25 percent of frozen embryos are truly considered excess, 3) patients are more likely to

about disposition of excess embryos are: cryopreservation for subsequent thawing and use to treat their infertility, donation to other infertile couples, or for research.[59] The same consequentialist reasoning about the discard issue at work in Case 1 also applies to Case 2 and heightens the obligation to be beneficent. Any reason to forgo such benefits must be strong enough to be overriding.

The most compelling reason to forego such benefits would be that a publically supported practice of embryo research would threaten society, in the words of Hans Jonas, "by the erosion of those moral values whose loss, caused by too ruthless a pursuit of scientific progress would make its most dazzling triumphs not worth having."[60] NBAC can focus on this classic statement of the moral limits of biomedical research with human subjects.[61] What

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discard embryos than donate to other couples, 4) at clinics where the option to donate embryos to research is given, couples are equally as likely to donate as to discard, and most significantly, 5) new technology allows longer culture of embryos (up to 5 days) and permits more quality assurance; embryos that do not appear normal and implantable are discarded and the remaining desirable embryos are frozen. The preliminary picture, which calls for more research, is that there are several pressures that will reduce the supply of excess embryos for research.

[59] The options to shape an optimal process for informed consent must be examined to heighten assurance that the embryos donated for research in Case 2 are ones that will be discarded and die.

[60] Jonas, H. (1969). Philosophical reflections on experimenting with human subjects. Daedalus, 98, 245.

[61] This is not an argument that an embryo is a human subject. It is a thought experiment using Jonas' moral wisdom as a mirror for reflection.

work does it do in relation to Case 2? The Jonas query is explored below in the section on considerations of non-maleficence.

We have seen so far that beneficence-based arguments heightened by the consequences of inevitable loss of opportunity to benefit, as in Case 1, are a first source of moral appeal to shape a consensus on access to donated embryos in research.

b) Autonomy-based considerations. Moral obligation based in respect for autonomy is a third moral similarity between Cases 1 and 2. If society ought to respect the autonomous and altruistic choices of donors in Case 1, it follows that the same imperative bears on Case 2, provided that the moral argument for access to embryos is strong enough to overcome objections. Parents who donate embryos want to contribute to knowledge about infertility, cancer, and genetic disorders. Such knowledge may yield solutions to relieve sickness and human suffering. These altruistic motives deserve respect as do the procreative intentions that caused the original creation of the embryos. IVF embryos are generated by decisions of couples who want to reproduce themselves. One must assume that they care about their embryos and enjoy the right to make decisions freely about options for disposition. These embryos exist within a web of caring relationships and are not isolated "research material." The federal and Louisiana bans on embryo research implicitly forbid

embryo donation for research. This effect contrasts with a right to make such donative decisions in privately supported research that is presently respected in other states.

Appeal to respect for the autonomous choices of donors of embryos is a second source of support for arguments favoring access.

c) Considerations based in non-maleficence. The clearest difference between Case 2 and Case 1 is that the fetus as a source of PSCs is dead and cannot be harmed by research activities. The donated embryo is a living organism that will die in the process of research rather than from being discarded altogether.

In moral terms, the major difference is: the abortion causes the death of the fetus; the research causes the death of the embryo. Is the researcher morally responsible in the sense of causing the death of a human being? Should any form of moral guilt attach to causing an embryo's death by research activities? Can embryos even be "harmed" in research?

Answers to these questions emerge from examination of prior questions. What kind or type of case is Case 2? What are the strengths and weaknesses of varying perspectives on the moral worth of embryos? How much protection ought society to give embryos in research? Finally, there is the Jonas query, i.e., will permitting embryo research, especially in the context of

Case 2, so erode moral values as to make even the "dazzling" goal of cell-directed therapy "not worth having?"

What kind of case is Case 2? If viable PSCs were derivable from donated embryos that were "allowed to die," [62] then Case 2 would fall clearly within Case 1 and a line of cases of cadaveric sources of organs and tissues, including fetal tissue. Cadaveric transplant cases have strong moral backing. However, when an embryo at the blastocyst stage stops developing and dies, one must assume the deterioration of the inner cell mass along with the PSCs within it. Case 2 is not in the cadaveric line of cases.

However, due to an origin within procreative intent, Case 2 is also not a case of creating embryos solely for research as are Cases 3 and 4. Cases 3 and 4 are in a new line of embryo cases raising the issue as to whether there can be two morally acceptable reasons for de novo creation of embryos: procreation and research. As long as the number of ova stimulated and fertilized in individual treatment were not being manipulated in order to produce an excess number of embryos for research, Case 2 ought not to be viewed within this new line of embryo cases.

[62] Two experts, Ted Thomas and Mark Hughes, with whom I discussed this question view it as highly improbable. They know of no research on the specific question but referred to the non-viability of DNA samples taken from 4-5 day old embryos in the process of dying. The NBAC should discuss whether the question of whether PSCs from dead embryos could be sufficiently viable for researdch ought to be scientifically studied.

In my view, if the integrity of the donative feature of Case 2 is authentic, then Case 2 is more like Case 1 than Case 3 or 4, because of the shared features already discussed, but especially due to the shared feature of donation. Moral authenticity would require at least two stages of the informed consent process. First is a consent process for the benefits and risks of one cycle of IVF, including the number of embryos likely to be fertilized. The decision to consent to treatment ought to be separated for a second stage of informed consent regarding cryopreservation and options for disposition of excess embryos: treatement of the couple's infertility, donation to other infertile couples, and donation for research. The moral relevance of intention to procreate and of parental concern for their embryos are, as argued by Annas, Caplan, and Elias, [63] an important and morally relevant feature of Case 2.

Moral status of embryos. Views about the moral status of embryos also influence the choice about whether Case 2 belongs to the line of cases represented by Cases 3 and 4. Do "excess" embryos donated for research have a lower moral worth because they have been selected for research? [64] If one views embryos as

[63] Annas, G.J., Caplan, A., Elias, S. (1996). The politics of hman embryo research - avoiding ethical gridlock. N Engl J Med 334, 1329-32.

[64] This is a complex question that is also related to the issue of relative moral worth of fetuses situated in the context of abortion. U.S. public policy is that there should be no difference in the degree of research protection owed to fetuses

having no moral standing at all, then the "moral worth" question is moot. If one believes that there are serious concerns in a moral viewpoint that objecting to Case 4 on the grounds that "it seems to cheapen the act of procreation and turn embryos into commodities,"[65] then one will focus strongly on the donative feature and the integrity of the consent process. Embryo research with embryos already available for research is easier to justify than creating embryos for research.[66]

The next draft of the paper will have an appendix on a spectrum of moral views on embryo research. What are human embryos morally considered? What degree of social protection should be given to human embryos? The work of the the Human Embryo Research Panel on the issue of moral status of embryos criticized "single criterion" approaches to personhood (e.g., genetic diploidy or self-concept). The Panel desired to take a broader and more "pluralistic" approach. Key sections describing this approach are worth reproducing here:

> ..[it] emphasizes a variety of distinct, intersecting, and mutually supporting considerations...the commencement of

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in the abortion context than in a context of continued gestation to delivery of the infant. This "Golden Rule" approach to fetal research is repeated in the embryo ban. The point is that the policy history within which NBAC is working assumes that there can be no difference between the moral worth of embryos, regardless of their source. This policy framework is open to moral challenge but it is the prevailing framework.

[65] Annas, et al., at footnote 63, p. 1331.

[66] In my view, the decisive factors in Cases 3 and 4 combine the weight of one's view of the moral status of embryos with proximity to scientific and clinical benefits.

> 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 other's liberty in relation to it) more compelling.
>
> 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 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 included genetic uniqueness, potential for full development, sentience, brain activity, and degree of cognitive development. Although none of these qualities is by itself sufficient to establish personhood, their developing presence in an entity increases its moral status until, at some point, full and equal protectability is required. [67]

The Panel noted similar reasoning by the U.S. Ethics Advisory Board in 1979, the Warnock Committee in the U.K. in 1984, and a Canadian commission in 1993.

An important article by Annas, Caplan, and Elias was critical of the Panel's report for several reasons.[68] They stated that the report lacked an underlying rationale that explained why the set of properties cited conferred moral worth. The lack of a rationale resulted, they argued, in not being able to know whether it is right to prohibit research after the 14 day appearance of the "primitive streak." A key section of the article is "An embryo has moral standing not so much for what it is (at conception or later) but because it is the result of procreative activity." (p. 1330) In this view, moral standing is

[67] See footnote 4, pp. 38-39.
[68] At footnote 63.

not only due to a "cluster of properties" that the embryo possesses but also from the "interests that potential parents and society bring to procreation and reproduction.."[69] This article shows that much more work can be done to construct a more satisfactory moral framework for embryo research that integrates the work of the Panel with other important perspectives. The NBAC report on PSC research should focus on this task.

Can Embryos Be Harmed in Research? The article by Annas, et al. makes an excellent point that the interests of parents and society in procreation can be damaged by morally unjustified embryo research. But can an embryo be harmed in research? one can concur with the Ethics Advisory Board's [70] position of respect (or even "profound respect") for the embryo, due to its human origins. At the same time, one can hold without contradiction that an experiment ending in an embryo's death cannot "harm" an embryo. The embryo is an organism with human origins, but it is without sentience and without a set of interests. Harm cannot be done to such an organism until the capacity for sentience has been established, which could only occur in the context of gestation. From this perspective there is a clear and "bright line" difference between the moral status of living children and embryos. To be sure, society does not permit comparable experiments with living children who are

[69] at footnote 63, p. 1131.

sentient and who have interests. However, society does permit Phase I trials in children with cancer; these trials carry a risk of morbidity and mortality. To the extent that living children are denied the benefits of embryo research, one can criticize current U.S. policy as overprotection of the embryo at the expense of children.

It is possible, of course, to damage an embryo in research. The damage would become "harmful" in the moral sense only if the embryo was transferred to a human uterus and a future sentient person was harmed by the damage once done to the embryo.[71] This possibility can be avoided by regulation forbidding the transfer to a human uterus or any laboratory equivalent of any embryo that had been involved in research.

Jonas' query. Embryo research has proceeded in the private sector without destroying society's moral values, despite its unregulated status and the wide diversity of practices permitted in infertility centers. It is relevant, however, that a too "ruthless" pursuit of embryo research could seriously threaten the values defended by Annas, et al. and others. If a researcher abruptly pursued Case 3, using animal ova to fuse with human

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[70] Ethics Advisory Board, op.cit., p. 101.

[71] This point is made by Helga Kuhse and Peter Singer in "Individuals, Humans, and Persons," in Singer, P., Kuhse, H., Buckle, S., et al., eds. (1990). Embryo Experimentation. Ethical, Legal, and Social Issues. (Cambridge: Cambridge University Press), p. 73.

cells to experiment with PSCs, one could rightly expect that the point of the Jonas query would be felt immediately. The slow and cautious approach to PSC research being followed by the NIH is advisable. Other Concerns Based in Nonmaleficence. The Human Embryo Research Panel carefully outlined a set of principles and guidelines[72] 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.

Case 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

[72] 1994, vol 1, pp. x-xi.

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 a form of 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. In U.S. public policy 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.

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. [73]

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.

IV. PUBLIC POLICY: SHOULD THE BAN BE PARTIALLY LIFTED?

NBAC should weigh the effect of the ban on embryo research

[73] Gearhart, Science 6 Nov 1998, 1061

on PSC and other valuable research. One effect is to give Geron-related labs a monopoly on Case 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 that favors a prospective 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.

3. The NBAC should explore a recommendation related to the ban that prefers a state-by-state approach to the moral status of the embryo, rather than the imposition of a federal ban.

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