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# DELIBERATING INCREMENTALLY ON HUMAN PLURIPOTENTIAL STEM CELL RESEARCH

by

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## INTRODUCTION [1]

The National Bioethics Advisory Commission (NBAC) faces major choices about its deliberations on ethical and public policy issues of human pluripotential stem cell (PSC) research. PSCs have the potential to develop into several (but not all) of the various cells in the body. PSCs are more specialized than the totipotent cells in a human blastocyst, each of which can develop into a total individual. In late 1998, supported by private funds, two groups of scientists concurrently reported laboratory culture and growth from PSCs of several cell lines. One group derived PSCs from tissue of aborted fetuses.[2] The other group derived human PSCs from

[1] The author wishes to acknowledge the expert help of my colleague, Franklin G. Miller, with prior drafts of this paper. The paper was developed through discussion with the NBAC staff, especially Andrew Siegel, Kathi Hanna, and Eric Meslin.

[2] 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.

excess embryos donated for research.[3] Due to controversy about the moral legitimacy of deriving PSCs from these sources, and for another reason,[4] President Clinton requested a "thorough" NBAC review of the issues "balancing all ethical and medical considerations."

The due date for a draft report is June 1, 1999. "How thorough is thorough?" and "What is the right balance...[of considerations]?" are fitting questions. The author's aim is to assist NBAC with these queries in public bioethics.[5]

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

[4] Letter to Harold Shapiro, November 14, 1998. President Clinton also requested NBAC to include implications of a reported attempt to fuse a human cell with a cow egg. Wade, N. (1998). Researchers claim embryonic cell mix of human and cow. New York Times, Nov. 12, p. A-1. Chairman Shapiro responded for NBAC to this aspect of the President's request by letter (November 20, 1998). The letter stressed that scientific evidence was insufficient to conclude whether the product of such fusion would be a human embryo. He referred to NBAC's position that creating a child by somatic cell nuclear transfer was in the near future morally unacceptable due to the high risk of harm. If such fusion did result in a chimeric organism that was not a human embryo, he saw no "new ethical problems" in using such organisms in research. He concluded that using non-human ova may avoid the risks and complications of obtaining human ova to create human embryos for research.

[5] Commissioners and readers will rightly be interested in the sources of the author's views in ethics. No one perspective or ethical theory can possibly satisfy the demands of the moral life. Several perspectives and methodologies in ethics, especially the dialogue between "principlism" and "casuistry", shape the author's

There are three major parts of this paper.

= Part I discusses three moral problems or concerns in PSC research and explores the scope of a full review. The problems are 1) the moral legitimacy of access to sources of PSCs, 2) considerations of uses of PSCs in research, and 3) the cumulative moral effects of the ban on federal funding of embryo research (FFER). Part I concludes with the history of FFER in a larger context of other controversies and

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views as expressed in this paper and the accompanying Appendix. Very complex moral problems that face society and government, such as human PSC and embryo research, require resources from several ethical perspectives and tools for ethics. In recent years, the author has with Franklin G. Miller, Joseph J. Fins, and Jonathan D. Moreno and others, sought to bring the resources of American pragmatism to bear upon the tasks of bioethics. The Appendix discusses the outlook of pragmatism in bioethics. At this point, it is worth marking a difference between a vulgar view (pragmatism is only concerned with what works) and a view embracing ethical principles but not treating them as fixed or timeless categories.

In 1922, John Dewey wrote a passage that could serve as a foreword to this paper: "..situations into which change and the unexpected enter are a challenge to intelligence to create new principles. Morals must be a growing science if it is to be a science at all, not merely because all truth has not yet been appropriated by the mind of man, but because life is a moving affair in which old moral truth ceases to apply. Principles are methods of inquiry and forecast which require verification by the event; and the time honored effort to assimilate morals to mathematics is only a way of bolstering up an old dogmatic authority, or putting a new one upon the throne of the old. But the experimental character of moral judgments does not mean complete uncertainty and fluidity. Principles exist as hypotheses with which to experiment. Human history is long. There is a long record of past experimentation in conduct, and there are cumulative verifications which give many principles a well-earned prestige. Lightly to disregard them is the height of foolishness. But social situations alter; and it is also foolish not to observe how old principles actually work under new conditions, and not to modify them so that they will be more effectual instruments in judging new cases." Dewey, J. (1988) Human Nature and Conduct. (Carbondale, IL: Southern Illiois University Press), pp. 164-5.

restrictions on federal funding of research at the beginning of human life.

= Part II discusses an alternative to a full review, i.e., an incremental or case-by-case approach to four sources of PSCs. This approach has strengths and weaknesses.

= Part III is an analysis of the moral effects of FFER and unreasonable limitations imposed by Congress on the federal regulations governing fetal research (FR). This Part proposes that principles of respect for the intrinsic value of life and distributive justice (augmented by principles of beneficence and utility) provide enough common moral ground from which to chart a public policy of incremental and regulated federal funding of PSC research and implementation of the federal regulations on FR as originally conceived by the National Commission for the Protection of Human Subjects. Given some sufficient conditions, these principles could also guide modifications of the ban on federal funding of PSC research derived from one source of embryos. The paper concludes with recommendations to NBAC drawn from the prior discussion.

Earlier national commissions and expert panels on fetal [6] and embryo [7] research compiled an impressive record. NBAC can build on this record in a new scientific context of stem cell biology and

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[6] 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); National Institutes of Health, Report of the Human Fetal Tissue Transplantation Research Panel, vol. 1, December 1988.

[7] Ethics Advisory Board, U.S. Dept. of Health, Education, and Welfare (1979). Report and Conclusions: Support of Research Involving Human In Vitro Fertilization and Embryo Transfer, (Washington, DC, US Government Printing Office); National Institutes of Health, Report of the Human Embryo Research Panel, vol. 1, Sept. 1994.

somatic cell nuclear transfer (SCNT) technology. Part II begins with NBAC's tasks in relation to PSC research.

## PART I. HUMAN PSC RESEARCH: CLINICAL PROMISE AND MORAL CONCERNS

### A. Human PSC Research

Human PSC research serves unprecedented scientific understanding of human cell development, gene function, and other biological questions.[8] Research with PSCs derived from fetal or embryonal (ES cells) sources is only one part of an exploding field of stem cell biology. Another part is research with stem cells found in adult animals.[9] Scientists are prepared to move beyond

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[8] Keller, G., Snodgrass, H.R. (1999). Human embryonic stem cells: the future is now. Nature Med 5, 151-2.

[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."

Richard Doerflinger focuses on the Bjornson study with adult mouse stem cells to suggest that the flexibility of these cells may make embryo-derived PSC research "irrelevant." Doerflinger Testimony, see footnote 14. This statement leaps to conclusions.

research in the mouse and higher animals [10] to novel experiments with human PSCs.

The clinical promise of PSC research is cell-replacement therapy for disorders caused by early cell death or injury. [11] As described below, there are many problems and inherent dangers to resolve before arriving at the threshold of clinical trials of PSC derived therapies. However, if realized, this approach to treatment could be of profound benefit to patients and society. Scientists envision effective treatment for the most common diseases, e.g., leukemia, diabetes, Alzheimer's disease, liver and heart disease, injuries to the spinal cord, and many more. Cell-replacement therapies could possibly supplant the "half-way" therapies (e.g., chemotherapy, organ transplants, hemodialysis,

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If it is morally acceptable to learn about the properties of PSCs derived from embryos, then the responsible scientific approach is to compare the properties of PSCs from various sources, including embryos, fetuses, and adults. If the embryonic source proves to have a higher risk of harm to animals or humans than other sources, then the former should not be used because of potential harm to patients. Doerflinger's statement probably implies that it is unethical to learn about the properties of PSCs derived from embryos.

[10] Thomson, J.A. et al. (1995). Isolation of a primate embryonic cell line. Proc Natl Acad Sci USA 92, 7844-48.

[11] Good summaries of the clinical potential of human PSCs derived from germinal fetal tissue and blastocysts of human embryos are: Gearhart, J., (1998), New potential for human embryonic stem cells. Science, 282, 1061-62; Pedersen, R.A. (1999). Embryonic cells for Medicine. Sci Amer, April, 69-73.

enzyme replacement, etc.) which are now the standard of care.[12] Thirty-three Nobel laureates' letter expressed these hopes to the President and members of Congress.[13]

Much basic research must precede any trials of therapy. Dr. Thomson [14] and other experts caution that perhaps five years will be needed to lay scientific and pre-clinical foundations for trials of cell-directed therapy. One of the highest goals in research in the near future will be to learn whether therapeutic uses of ES cells carry dangers of tumorigenesis that ought not be risked.[15]

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[12] These advances promote 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.

[13] 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 permit federally funded researchers to work with PSCs.

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

[15] "Mouse ES cells are tumorigenic, growing into teratomas or teratorcarinomas when injected anywhere in the adult mouse. There is no reason to believe that human ES cells will not be tumorigenic in humans. Whatever means we use to separate the undifferentiated ES cells from the desired, differentiated progeny to be injected, we will have to be abvolutely sure that the separation is complete. As yet, we do not know the minimal number of ES cells necessary to

Continued research in the mouse and new research with ES cell lines should should resolve this issue one way or the other. There is consensus in the scientific community that support by the National Institutes of Health (NIH) and the National Science Foundation (NSF) of PSC research will both enrich and shorten preparation for clinical trials of cell-replacement therapies.

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 moral legitimacy of access to sources of PSCs, considerations of uses of PSCs in research, and the moral effects of the current federal ban on embryo research.

1. Access to Sources of PSCs.

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form a tumor or the length of time necessary for tumor development. The answers to these questions will not come from experiments with mice ecause mice are too shortlived to provide an adequate test. It is entirely possible that we will have to provide some genetically designed fail-safe mechanism, a `suicide' gene, which will enable us to destroy transplanted cells if they become tumorigenic." Solter, D., Gearhart J. (1999). Putting stem cells to work. Science, 282, 1468.

Table 1 ranks access to sources of PSCs by degree of moral and legal acceptability and of moral controversy.[16] The discussion refers to access to sources as "Cases" 1, 2, 3, and 4.

Table 1. Sources For Deriving PSCs

Case 1. PSCs derived from human fetal tissue following elective abortion (e.g., Gearhart research).[17]

Case 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).[18]

Case 3. PSCs to be derived from human (or hybrid) embryos generated asexually by SCNT (using enucleated human or animal ova).[19]

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[16] These questions about degree of controversiality could clearly be studied in public opinion. The results are crucial to public policy formation. Public policy making that ignores public opinion courts disaster, not because it should always cravenly follow public opinion, but because it is prudent to legislate against reliable knowledge of what the public thinks about a particular issue.

[17] See footnote 2 above.

[18] See footnote 3 above.

[19] This work has not yet been done in the mouse. (Brigid Hogan, personal communication, March 12, 1999) 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.

Case 4. PSCs to be derived from human embryos created, with informed consent, from donated gametes for the sole purpose of research.[20]

Overview of the paper.. Federal agencies may not legally fund any research to derive PSCs from embryos, although "therapeutic" embryro research is permitted by the language of the ban.[21] Part II explores an incremental approach to the ethical issues raised by access to these sources. An incremental approach could also guide the reform of federal science policy on funding sources of PSCs.

Federal policy is already changing to permit some funding of PSC research. The General Counsel, Department of Health and Human Services (DHHS) has advised [22] the NIH that it can legally fund "downstream" research with PSCs derived by private funds but not

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[20] 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.

[21] The language of the ban on FFER is modelled after the language of an earlier Congressional ban on fetal research, which permits research designed to "enhance the well-being or meet the health needs of the fetus or enhance the probability of its survival to viability.." The Health Research Act of 1985, Sec. 498 (a) (1). 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 such therapeutic experiments.

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

derivation of PSCs at the blastocyst stage. This legal opinion is controversial and silent on the moral issues discussed in the next section. Nevertheless, if a) Congress allows the legal opinion to stand, b) the NIH successfully oversees and guides the new step,[23] and c) important scientific and pre-clinical information takes the field to the threshold of clinical trials and it can be shown clearly that access to a source of PSCs in Case 2 is the only way to cross that threshold, then a legal modification of the ban could be justifiable. Part III of the paper gives a moral argument based in part on these conditions for federal funding of access to embryos in Case 2. The argument makes two assumptions: first, such conditions will develop in the near future; second, there may be other other reasonable alternatives to living human embryos as sources of ES cells required for clinical trials.

[23] Draft NIH Guidelines for Research Involving Pluripotent Stem Cell Research. For discussion at the meeting of the Working Group of the Advisory Committee to the Director, NIH. April 8, 1999. Without using the terms "ethical" or "moral", these guidelines state that NIH-funded investigators who use PSCs "should" do so only if suppliers of such cells have documented that: 1) the PSCs were derived from excess embryos donated in the context of infertility treatment, 2) were donated in the context of practices of informed consent with safeguards against undue or "even subtle" pressure to donate, and 3) that the PSCs were not derived from embryos created for research purposes. These carefully worded guidelines assume, without further argument, moral reasons for prescribing these special duties.

The discussion will show that Cases 3 and 4 pose many more difficult issues for federal funding for access to embryos than those that arise in Case 2. Human embryos have not yet been created by SCNT, making it premature to deliberate on Case 3. Would these SCNT-created embryos be biologically identical or different from those in Cases 2 and 4? More research in animals must prepare the way for SCNT research with human cells. The arguments for federal funding of access in Case 4 are stronger today than in 1994 because of PSC research. However, using federal funds to generate embryo only for research is controversial enough to overwhelm rational debate about federal funding of deriving ES cells in 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.

Transition: Can Access Be Separated from Uses?

Before a section on uses, the "separability" of the issue of access to embryos ought to be examined. The NIH has already officially separated the issue of access from uses. The agency's legal advice was altogether silent on ethical issues. Nonetheless,

the memorandum loudly begs the question of the morality of derivation.[24]

The memorandum makes moral sense only on a premise that the legal permissibility of deriving embryos in some states with private funds is a moral floor for derivation. This paper adopts a premise, among others, that the morality of access to embryos is logically and morally prior to the issue of uses of PSCs in research. Further, a social practice of access to embryos (however created) for research requires a persuasive moral argument to justify it in a society and a Congress now divided over the subject.

Ironically, the lack of a unified national policy for embryo research makes it possible for the NIH to take this direction. The history of Congressional inaction on infertility and the limitation of the ban to *federal* funding leaves activities in the private sector unregulated. A variety of privately funded practices in embryo research operate at the margins of public life.

[24] Some members of Congress responded to the moral as well as the legal question. Section 3 of this part of the paper discusses their position.

Federal law does not prohibit embryo research in the private sector. The legality of PSC research in the various states is a complex topic.[25] Andrews writes:[26]

> In 24 states, there are no laws specifically addressing research on embryos and fetuses.[27] In those states, embryo stem cell research is not banned. However, other legal precedents covering informed consent, privacy, and commercialization, come into play.

From a premise of constitutional protection of the choice of elective abortion, in 1990 the Human Fetal Tissue Transplantation

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[25] Based on her latest research on the subject, Andrews writes: "...statutory and court precedents dealing with embryo and fetal research, abortion, organ transplant, and payment for body tissue all have ramifications for work involving embryo stem cells. Yet no two states have identical laws covering these procedures.

Some type of embryo stem cell research is permissible in virtually every state. [North Dakota has statutes that could be used to prohibit both the Thomson and Gearhart technique] Yet, because of differences in state laws, certain states would ban the collection of stem cells from embryos that were created through in vitro fertilization. [Florida, Louisiana, Maine, Massachusetts, Michigan, Minnesota, North Dakota, Pennsylvania, and Rhode Island] In other states, a prohibition would only apply to the isolation of stem cells from aborted embryos and fetuses." [Arizona, Indiana, North Dakota, Oklahoma, and South Dakota]. See: Andrews, L.B. (1999). State regulation of Embryo Stem Cell research [draft]. NBAC Commissioned Paper, p. 1 and notes.

[26] See footnote 23 above, p. 3.

[27] These states are: Alabama, Colorado, Connecticut, Delaware, District of Columbia, Georgia, Hawaii, Idaho, Iowa, Kansas, Maryland, Mississippi, Nevada, New Jersey, New York, North Carolina, Oregon, South Carolina, Texas, Vermont, Virgina, Washington, West Virginia, and Wisconsin.

Research Panel [28] argued that it could separate its deliberations on the morality of the uses of fetal tissue from the morality of abortion. The Panel took no explicit position on the morality of abortion.[29] In theory, NBAC could take the same approach with embryo research.

The approach's main appeal is reduced controversy. However, there are important reasons reasons for NBAC to be less confident in using this approach with embryo research. The first reason arises from variability in the law as a trustworthy floor for morality.

Law does express moral beliefs and values. Rightly seen, law is a floor for morally permissible acts but not a ceiling for moral ideals. Nonetheless, in houses and in law, one finds strong and weak floors. Different elements contribute to these strengths and weaknesses.

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[28] See footnote 6 above, Human Fetal Transplantation Research Panel (1990) vol. 1, question 1, pp. 1-2.

[29] A prior national commission essentially decided not to defend the morality of abortion in the context of a report on genetic counseling and screening. The commission was, however, very critical of the use of prenatal diagnosis for sex selection only. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research. (1983). Screening and Counseling for Genetic Conditions. (Washington, DC: U.S. Government Printing Office), p. 58.

Absence of legal prohibition is a weak floor for moral acceptability of access to embryos compared with the strength of laws that bar unwarranted intrusions into a lawful choice, e.g., federal court decisions and state laws protecting the liberty to choose abortion. Law does not bar some activities and choices open to serious moral challenge, such as sex selection by prenatal diagnosis. Embryo research is open to serious moral challenge,[30] but this activity can be morally defended and justified.

Collective moral experience and scholarly ethical reflection (on both sides of the issue) can be likened to strength-giving elements. These elements are plentiful in the floor of law on abortion compared with federal or state law on embryo research. Congress first banned federal funds for embryo research in 1995 with no careful attention to consequences for patients, science, or society. In 1994, Andrews wrote: "embryo research *per se* has rarely been the subject of state legislative scrutiny."[31] There has since clearly been more scrutiny and legislative activity in several

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[30] My moral viewpoint does not equate embryo research with prenatal diagnosis for sex selection. This statement about embryo research being "open to moral challenge" acknowledges the seriousness of moral views holding that society ought to protect human embryos from research activities. The relevant issue for public policy is the warranted degree of protection.

[31] Andrews, L. (1994). State regulation of embryo research. In National Institutes of Health, Papers Commissioned for the Human Embryo Research Panel, vol. 2, p. 298.

states. However, as reported by Andrews, state laws relevant to PSC research vary widely. [32]

For these reasons, NBAC cannot proceed on the basis of absence of state law on embryo research with as much confidence to work on PSC research as prior panels and commissions were able to do from a basis in law on abortion. If NBAC did so proceed, an objection would surely be that NBAC avoided the moral debate on access but smuggled in a permissive position beneath a shaky legal argument. Access to live embryos for research requires a stronger moral defense than one afforded by an absence of law.

Also, advances in stem cell biology have dramatically changed the scientific context. NBAC can contribute an ethical analysis of embryo research in this new context and also account for several criticisms of the moral perspective adopted by the NIH Human Embryo Panel in 1994.[33] Can the NBAC come to consensus on access to embryos for research? This question must be explored. Whatever the outcome, the NBAC can then assess public policy recommendations that it desires to make.

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[32] See footnote 23 above, p. 13.

[33] See especially, Charo, RA (1995). The hunting of the snark: the moral status of embryos, right-to-lifers, and third world women. Stanford Law & Policy Rev 6, 11-27; and Annas, G.J., Caplan, A., Elias, S. (1996). The politics of human embryo research - avoiding ethical gridlock. N Engl J Med 334, 1329-32.

2. Uses of PSCs in Research

The argument is that the morality of access to sources of PSCs is logically and morally prior to questions about uses. Concerns about uses of PSCs are beside the point if it is morally unacceptable to access any sources, e.g., in Cases 1-4. Nonetheless, is it morally acceptable for scientists to access all *four* sources for PSCs? Part II offers ethical and public policy reasons why NBAC can be more confident about the moral acceptability and rationale for federal funding of access to sources of PSCs in Case 1 and 2 than it can be --at this time-- to sources in Cases 3 and 4.

The rest of this section on uses assumes the arguments of Part II and a premise that there are no overriding moral reasons why society or patients must forgo benefits from research in Cases 1 and 2. There are good reasons -- scientific, ethical, and political -- for NBAC to treat uses of PSCs derived in Cases 3 and 4 with far more restraint and caution.

Ideally, reflection on permissible uses would occur in a cultural framework of settled ethical and legal boundaries for embryo research, such as exist in the United Kingdom. However, the United States has two universes of science and the funding of science: public and private. Descriptively, when it comes to

embryo research, these divided universes respectively permit an overly permissive morality in the private sector and impose an overly protective morality in the public sector.[34] Nonetheless, as a bioethics commission, NBAC is obliged to address ethical issues as if it were possible for moral purposes to unify these two universes.[35] NBAC's work on the ethics of PSC research could eventually contribute to a unified public policy on embryo research. However, if NBAC's public policy recommendations are to be useful in the present context, it must account for the reality of these two dichotomous moral spheres within one nation.

Three Types of Uses of PSCs in Research. Dr. Varmus [36] and others[37] describe three general areas of research uses of PSCs: 1) studying the efficiency and regulation of human PSC and cell line differentiation in culture, 2) studying toxicity and beneficial effects in the context of drug development, and 3) growing cells of

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[34] Insofar as this division of moralities is a political compromise to ameliorate conflict, the political advantages to the public sector are far less secure when the promise of curing diseases is tangible.

[35] Such unification was indeed accomplished in the early debates about DNA research, which led to the creation the NIH's Recombinant Advisory Committee (RAC).

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

[37] See footnote 7 above.

different types for transplants to repair or replace patients' injured or dying cells.

Questions of scientific merit, utility, and linkage to larger disputes ought to be raised about all proposed uses of embryos in research. Deliberation ought to focus first on issues of scientific justification and utility and secondly on potential 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 of number is related to the supply of embryos for research. Supply is shaped by practices in infertility treatment centers and the percentage of IVF embryos that will be eventually discarded. [38]

Some proposed uses of PSCs are linked to large and unresolved controversies still facing society and policy makers. For example, if NBAC "thoroughly" reviewed Cases 3 and 4, it would need to revisit fully the debates about human cloning and human germ-line gene transfer.

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[38] Part II gives some preliminary information on this situation which ought to cause concern but requires more research for definitive results.

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. In terms of preparation for clinical trials of cell-replacement therapy in human beings, the immediate uses can be described as the first of three stages. Stage 1, a purely scientific phase, aims at knowledge about properties of human PSCs and cell lines derived from available sources of PSCs, i.e., embryonic stem (ES) cells and fetal germ (EG) cells. [39] This knowledge is necessary to prepare for Stage 2, a pre-clinical phase in which answers to the desirability of trials in humans are pursued with animals as well as in the laboratory. Stage 2 also involves the choice of one or more candidate diseases for whic to mount clinical trials. If a consensus can be reached

[39] "Many questions related to the possible therapeutic use of human ES cells have not been addressed in mouse ES cells simply because of the lack of interest. Fortunately, our understanding of the molecular pathways of differentiation and the molecules that mark specific cell types is extensive. This knowledge should help us to answer the following questions: Can human ES cells be forced to differentiate along a desired pathway? Can we make all ES cells in a culture simultaneously develop along that pathway? What exactly are the intermediary cell types and how can they be defined? Which markers and whic methods can be used to sort out the desired cell types? Human ES cell lines will providemany of the answers to these questions." Solter and Gearhart, see footnote 15 above, p. 1469.

on the pre-clinical and ethical considerations of the first trial or trials in humans, Stage 3 is a series of clinical trials in humans of investigational cell-replacement therapies. Stage 2 aims at the scientific feasibility and moral justification of human trials. Stage 3 aims to answer the question: is cell-replacement therapy safe and effective in human beings?[40]

Relevant to Stage 1, Dr. Brigid Hogan [41] noted differences in DNA between cells derived from EGs and 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. A related task is to study differences between ES and EG cell lines and those grown from stem cells recovered from adults or children.[42]

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[40] Stage 3 encompasses a series of phases (One through Four) of clinical trials that scientists describe as needed to prove safety and efficacy first in small numbers and later in populations.

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

[42] See footnote 8 above.

Dr. Gearhart [43] outlined some straightforward 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.

If it is possible to generate human embryos by SCNT, and Case 3 is feasible, many of the same studies described above need to be repeated. Would there be differences between the properties of PSCs derived from SCNT-generated human embryos and cell lines grown from EG and ES cells? As discussed by Solter and Gearhart, "at the outset, it was realized that the full therapeutic potential of ES cells will depend on using ES cell lines derived from the patient's own cells for tissue replacement." [44] Eventually, studies will be needed of the feasibility of autologous cell replacement therapy to avoid the graft-vs.-host reaction. Ought these embryos, created by cloning technology, be regarded with the same degree of respect

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[43] at note 1, 1062.

[44] See footnote 15 above, p. 1469.

deserved by sexually created embryos? This question has already surfaced in NBAC discussion. [45] Solter and Gearhart raise the basic ethical question as to whether creating embryos by SCNT to be used only to derive ES cells is permissible.[46] The answers to these questions needs careful reflection related in part 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.[47] 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 domain of Case 4, and is an activity similar to studying when alleles begin to express DNA in the embryo in a context of understanding the origins of particular diseases.[48]

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

[46] They write: "Society must decide whether the therapeutic benefits justify denying full development to the constructed embryos." See footnote 15 above, p. 1469.

[47] This approach to "large panels" of cell lines is envisioned by Solter and Gearhart as a way to circumvent the necessity of Case 3, "so that everybody will find a match or by eliminating or altering the histocompatiability antigens, thus creating `universal' donor lines." See footnote 15 above,p. 1469.

[48] 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

Infertility centers, using private funds, now create embryos to study the viability of frozen ova or to improve the medium in which embryos grow after IVF. We must expect that some privately funded research with PSCs will occur in the context of Case 4. This work is regulated only by the ethics of professionals. This source of protection is at best porous in a current marketplace of largely unmanaged competition that can overwhelm the integrity of professional self-regulation in medicine and research.[49] Shaping a unified policy and regulatory oversight for U.S. embryo and fetal research is a long-term and daunting task. This task is almost as daunting as extending constitutionally guaranteed protections to all human subjects of research and to expand regulation and

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gene is the key factor in Shah-Waardenburg syndrome. A paper was prepared for the Human Embryo Research Panel in support of a case for recruiting embryos from couples whose children were at risk for cancers caused by genomic imprinting: 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 the disease process caused by genomic imprinting in the embryo could eventually be useful in diagnosis and treatment of these diseases in children.

[49] See especially Spece R.G, Shimm, D.S., Buchanan, A.E. (1996). Conflicts of Interest in Clinical Practice and Research. (New York: Oxford University Press).

oversight of practices in research with human subjects to the private as well as public realms.[50]

PSCs may have potent uses in research on human gene transfer in the hope of treating genetic disorders. Will PSC-assisted gene transfer resolve major technical problems in using exogenous vectors to transport corrective DNA to target sites? Dr. Austin Smith's testimony to NBAC [51] and a NIH discussion paper on cloning point in this direction.[52] Pincus, et al.,[53] discuss the use of neural stem cells that persist in the adult brain as a vector to do gene therapy in neurodegenerative diseases. Their review cites a successful neonatal experiment in a mouse model for mucopolysaccharidosis.[54] In the context of human somatic cell gene transfer, the use of PSCs raises no new ethical questions. Dr.

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[50] This task was discussed in a report for NBAC by the author: "Location of OPRR within the NIH: Problems of Status and Independent Authority," November 27, 1997. (NBAC document).

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

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

[53] Pincus, D.W., Goodman, R.R., Fraser, R.A.R., et al. (1998) Neural stem and progenitor cells: a strategy for gene therapy and brain repair. Neurosurgery 42, 858-68.

[54] Snyder, E.Y., Taylor, R.M., Wolfe J.H. (1995) Neural progenitor cell engraftment corrects lysosomal storate throughout the MPS VII mouse brain. Nature 374, 367-70.

Erik Parens' testimony to NBAC notes how PSC research will converge into experiments to treat the DNA of human embryos and prevent genetic diseases in children-to-be. [55] A truly "thorough" and far-ranging review of PSC research would examine the scientific and ethical issues in this vast topic.

In summary, the most immediate uses of PSCs in research follow derivation in Cases 1 and 2. Future uses of PSCs derived from embryos in Cases 3 and 4 are dependent on 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 for deriving PSCs from embryos in Cases 3 and 4 will need safeguards against transferring a SCNT-created human embryo for implantation 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 review authority over any proposed therapeutic modifications to DNA in gametes or embryos.[56]

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[55] Parens, E., Testimony to NBAC, Jan. 19, 1999, p. 98. As members of an AAAS taskforce, Dr. Parens and Eric Juengst are presently cooperating on a promising approach to clarify the older concept of "human germline gene therapy" within a more accurate framework of "inheritable genetic modifications." See:

[56]

When bodies (NBAC or IRBs) are considering proposed uses or protocols for PSC research, they may refer to Table 2, as well as to guidelines of the NIH on funding PSC research.[57]

Table 2. Points to Consider For:
Proposals or Protocols for PSC Research

1. How will the PSCs be derived?

2. Does the investigator have a protocol and IRB approval for access to this source? A consent process that has been IRB approved?

3. What is the minimal number of fetuses/embryos required to do the study?

4. If the investigator will access fetal tissue, are the project and the consent process in compliance with Public Law 103-43, Part II?

5. Is the research design the best possible, given the state of the art?

6. Will the research plan yield answers to the questions being posed?

7. If the PSCs in this project will be derived by SCNT, the investigator must stipulate that no embryo made by cloning technology could be used for reproduction.

8. If the PSCs in this project are to be used in the context of a clinical trial of human gene transfer, the investigator must stipulate knowledge that approval of the FDA/NIH-RAC is required.

[57] Cited at footnote 22 above. These guidelines have been submitted to the Federal Register for comment.

3. The Ban on Federally Funded Embryo Research (FFER)

After the elections of 1993, Congress lifted a moratorium on federal funding of IVF research that required the approval of an Ethics Advisory Board.[58] After the elections of 1994, a new Congress banned FFER and ended a brief period of NIH hopes to fund improvements of IVF and other projects involving human embryos.[59]

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[58] The NIH Revitalization Act nullified the requirement for an Ethics Advisory Board approval for protocols involving IVF. [Pub. L. No 103-43, 121(c) (June 10,1993)] This law opened the door for federal funding of embryo research, but NIH appropriately chose a step by step process, beginning with the appointment of the NIH Human Embryo Research Panel in February, 1994, to consider the ethical, legal, and social implications of human embryo research. The EAB (1978-79) had considered only the issues related to research designed to improve the technique of IVF and its outcomes. The report of the EAB (see footnote 7 above) stressed that another body would need to consider the larger implications of what we are calling here Case 2 and Case 4 issues. Although it would have been legal in 1993 for the NIH to fund human embryo research, especially studies designed to improve the composition of the culture medium for IVF embryos, NIH did not do so either before, during, or in the period between the Panel's final report and the ban on federal funding. NIH did receive protocols for this purpose, but limited funding only the aspects of the studies involving animal embryos, being aware of the opposition to funding activities involving human embryos by a sizeable number of conservative members of Congress. (Personal communication: George Gaines, NICHD. April 29, 1999) Although President Clinton announced his acceptance of research with excess embryos, which would have been legal in this period, the NIH did not fund this type of research and has never done so.

[59] Pub. L. No. 104-99, January 26, 1996, enacted a ban on 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.." The term "human embryo" in the statute is defined as "any organism..

This section will locate the ban on FFER in the history of bioethics in government.

Turmoil over PSC research in moral and public policy research is a new chapter in a long history. Since 1973, Congress[60] has adopted strong, and in my view, overly protectionist policies regarding research activities at the beginning of human life. No other ethical issues in research rise to the same level of public controversy.[61] Commissioners and the public need to understand this

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that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells." This ban was pertinent to FY 1996 funds. The Omnibus Consolidated Fiscal Year 1997 Appropriations Act (Pub. L. No. 104-208) adopted identical language. The ban is transitory in the sense that it is revisited each year when the language of the NIH appropriations bill is considered.

[60] Congress was supported in this direction by the Reagan and Bush Administrations. The Clinton Adminstration rescinded the moratorium on fetal tissue transplant research and has been moderate on embryo research, in that it is willing to support Case 2 research activities.

[61] These protectionist policies, aside from the studied compromises of the National Commission (with a plan for ongoing conflict resolution) have been adopted in an often rancorous and alienated political culture. The role of public bioethics in American culture is to temper emotions and premature moral judgments that often mark political interests and to balance these interests with those of science, the public, and ethical and legal considerations. However, without a permanent presence in government of a body to work on the ethics of research, the task of creating new public bioethics bodies (like the EAB) can be overwhelmed by political considerations. NBAC's mandate to consider what national resources are necessary to optimize the protection of human subjects of research is directly related to such issues.

history to have perspective on the future of PSC research in the federal sector.[62] The history includes Congressional restrictions on federal funding for fetal research (FR), human fetal tissue transplant research (FTTR), a pattern of Congressional inaction regarding infertility research, and the broader effects of the ban on FFER that prevent NIH and NSF involvement in basic research to gain knowledge relevant to cancers and other genetic diseases, infertility, contraceptive development and other areas.[63]

Federal Regulation and Law on FR [64]

Justice Blackmun and a majority of the Supreme Court ruled in Roe v. Wade [65] that a fetus is not a person in the context of

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[62] As well as the ways in which NBAC's work on PSC research (in the political context of this Congress and Administration) intersects with issues of long-range reform of the entire system of protection of human subjects of research and consideration -- at the national level -- of long-range ethical issues posed by research for society and its political and legal institutions.

[63] NBAC must also grapple with several long standing needs with origins in the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: e.g., for a permanent national ethics committee for research ethics, to extend protection of human subjects to the private sector, and the place of the Office for Protection from Research Risks (OPRR) in government.

[64] A very informative history of events prior to 1988 is found in Lehrman, D. (1988). Summary. Fetal Research and Fetal Tissue Research. (Washington, DC: American Association of Medical Colleges).

[65] Roe v. Wade, 410 U.S. 113 (1973).

constitutionally protected rights. In the wake of the ruling, members of Congress were concerned about possible research exploitation of fetuses to be aborted.[66] In 1974, the law mandating IRBs also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[67] The first mandate of Congress to the Commission was for ethical and public policy guidelines for FR. The Commission's recommendations would become federal regulations. The Commission completed its work on FR within four months.[68]

The ethical framework of its report was a three-sided compromise between liberal and conservative views on fetal research, with an added feature (to facilitate the compromise) for a national Ethics Advisory Board (EAB) to review and resolve

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[66] News stories from abroad about research with live fetuses ex utero raised questions about NIH funding of these projects. A a demonstration led by Eunice Shriver, NIH's leaders denied such funding. The NIH then imposed a moratorium. Cohn, V. (1973). NIH vowsnot to fund fetus work. Washington Post, April 13, A-1. The moratorium was continued by the law creating the National Commission and was to remain until the commission made recommendations. The law prohibited "research (conducted or supported by DHEW) in the United States or abroad on a living human fetus, before or after the induced abortion of such fetus, unless such research is done for the purpose of assuring the survival of such fetus." (section 213)

[67] Hereinafter referred to as the National Commission or the Commission.

[68] See footnote 6 above for citation of the report, submitted on May 1, 1975

problems in future protocols on FR.[69] First, guided by the

[69] A crucial aspect of the EAB's work, as envisioned by the Commission, was to develop further national policy on FR and other issues of human subjects research. There is a connection between the Commission's early work -- and the impasses that it reached in attempting to compromise on FR -- and its vision of an EAB. This is the best point in the paper to relate this history.

The Belmont Report, adopted by the Commission in 1979, is the most authoritative American source for ethical guidance for research with human subjects. It opens as follows: "Scientific reseach has produced substantial benefits. It has also posed some troubling questions." Since 1966 [Levine, R.J. (1988). Ethics and Regulation of Clinical Research, 2nd ed.] a federal policy restricting research activities with human subjects has been in effect. The policy has two goals: 1) to protect human subjects and investigators, and 2) to question whether particular research activities ought to be done at all and to resolve disputes concerning these questions. The United States was the first nation with a federal law (Public Law 93-348) to support a local and national process to achieve both policy goals.

Locally, an IRB has authority to approve or reject a proposal or to alter it to reduce risks or increase benefits. IRB's were not designed to consider the "long-range effects" of research on society or morality (45 CFR 46. 111 (2) such as societal effects of FR. This task was to be done by "one or more" EABs to be established by the Secretary, DHEW (45 CFR 46.204 (a). This two-tiered process of local (IRB) and national (EAB) oversight of research activities was envisioned as sufficient to protect both human subjects and the freedom of research, given a need to restrict some activities in the public interest.

Belmont's opening words rest on two premises. One was clearly stated (i.e., that research had benefited society). The second premise was unstated, regarding the role of scientific freedom in what outhgt to be done about the "troubling ethical questions" posed by research. This premise was that any restrictions on freedom of research would be justified only after careful study and debate, with limits openly arrived at in a democratic and legal process. Protection of scientific freedom was one of the key elements in early reforms of U.S. research ethics.

How would the "troubling ethical questions" faced by the National Commission be actually addressed? These were about research with vulnerable populations, like the fetus and pregnant

principle of beneficence, the Commission encouraged FR because of its benefits.[70] Any reasonable liberal view on FR could support the first point. Second, the Commission sharply restricted FR under an equality-of-protection principle, especially to protect fetuses to be aborted from exploitation. The second point was a bold specification of a conservative viewpoint that was incompatible

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women, children, prisoners, and institutionalized persons with mental disabilities. Belmont's approach was to discuss these questions guided by general ethical principles (i.e., respect for persons, beneficence, and justice). However the National Commission itself, according its own report (see footnote 6, 1975:67) could agree on the "validity" of a principle but not on its application in a specific protocol of FR. At the time, philosopher Stephen Toulmin (Appendix, 1976:15) wrote that the Commission's task was to "keep a watchful eye" on the development of "case law" and "precedents" that would actually grow up in FR activities governed by decisions of local IRBs. This analogy to lower and higher courts gives insight into Toulmin's and the Commission's reasoning (as well as that of Donald Chalkley, the founding Director of the Office of Protection from Research Risks) about the relationship between IRBs and the EAB.

The Commission's vision for an EAB was as a permanent national resource. Its role would be to study, debate, and recommend approaches to resolve controversial research proposals referred by a local IRB or by the Secretary, DHEW. Also, Congress had created the Commission against a background of government appreciation of the "benefit of a long partnership with science, not a long record of hostility" [Dupree, A.H. (1957). Science in the Federal Government. Cambridge, MA: Belknap Press, 381.] In the 1980's and beyond, influenced mainly by abortion politics, Congress reversed this tradition in respect to reproductive medicine and human genetics; it became hostile to science at the beginnning of life and substituted what it could legitimately control, i.e., by imposing bans on federal funding.

[70] E.g., in developing a vaccine against rubella, amniocentesis, treatment of Rh isoimmunization disease, and respiratory distress syndrome.

with a utilitarian ethos previously dominating U.S. research practices which had guided investigative research with living fetuses ex utero.[71] The Commission, even in the face of Roe v. Wade, specified that societal protection of human subjects of research ought to be extended to fetuses, including fetuses in the context of abortion.[72] To make this compromise work in actual

[71] One example of such strictly utilitarian investigative research - designed to increase biomedical knowledge but not to benefit the fetus involved - was a 1963 study done in the U.S. Scientists immersed fifteen fetuses in salt solution to learn if they could absorb oxygen through their skin. One fetus survived for twenty-two hours. The knowledge gained by the experiment contributed to the design of artificial life-support systems for premature infants. [Goodlin, R.D. (1963). Cutaneous respriation in a fetal incubator. Am J Ob & Gyn 86, 571-79.] The report that triggered the demonstration at the NIH was of an experiment in Finland. Researchers perfused the heads of eight fetuses after hysterotomy abortion, to learn if the fetal brain could metabolize ketone bodies. This study was the only way by which the researchers could confirm findings from animal research. [Adam, P.A.J., et. al (1973). Cerebral oxidation of glucose and D-BOH Butyrate by the isolated perfused fetal head. Ped Res 7, 309 - abstract.

[72] How did the Commission come to this second point of the compromise, especially in the legal context of Roe v. Wade? If the fetus is not a person in the constitutional sense, why do fetuses deserve equal protection in research activities? The answer lies in the collective views of the Commissioners, who were ready to compromise for a number of reasons and also in the influence of bioethicists of this period on the Commission.

The Commission's report drew upon the work of several ethicists who wrote commissioned papers and testified. In my view, Richard McCormick and LeRoy Walters had the greatest influence on Stephen Toulmin's draft of the Commission's recommendations. A leading Catholic moral theologian, McCormick's view was that "the fetus is a fellow human being, and ought to be treated...exactly as one treats a child." McCormick, R. (1976). Experimentation on the fetus. Policy Proposals. In Appendix to the Report and

Recommendations: Research on the Fetus. Washington, DC: U.S. Government Printing Office, HEW Publication No. (OS) 76-128:5:4. McCormick argued for a very limited approach to FR with reasons he used in approving parental proxy consent for investigative research with children. McCormick R. (1974). Proxy consent in the experimentation situation. Persp Biol & Med 18, 2-20. He extended this reasoning to FR in a few examples of "tragic" abortions he found morally acceptable. McCormick, R. (1981). How Brave a New World? (Washington, DC: Georgetown University Press), p. 76. McCormick would permit FR in such a context, provided that "there is no discernible risk, no notable pain, no notable inconvenience, and ... promise of considerable benefit." McCormick, 1976, op. cit., p. 8. McCormick's term "no discernible risk" later evolved into the category of "minimal risk" in the Commission's deliberations about research with children. The meaning of minimal risk continues to be controversial and widely challenged.

Walters advised use of a principle of equality of protection in research, whether fetuses were destined for abortion or delivery. Under this "Golden Rule" idea, researchers could not impose a higher risk with a fetus to be aborted than they would with a fetus to be delivered. See Walters, L. (1976). Op. cit., 8:1-18.

Similar to the "Peel Report" (1972) in the U.K., Sisela Bok (1976:2:1-8) favored selectively higher research risks before 18 weeks in the context of abortion. She gave four reasons for society's protection of human life: 1) to protect victims, 2) to protect agents from brutalization and criminalization, 3) to protect a victim's family from grief and loss, and 4) to protect society from greater harm that would follow from permissive killing. She argued that up to a point well before viability such reasons have no moral relevance to fetuses, because claims for the "humanity" of the early fetus fail to make sense.

Toulmin preferred McCormick's position to Bok's, because it opened a way conceptually for those giving primary rights to the fetus to accept FR. However, along with McCormick's position came his risk standard and the underlying premise that fetuses ought to be treated equally, as "fellow human beings."

In the face of this compromise, the Commission grappled with the logical consequence that one ought to place fetuses to be delivered at the same risk in investigative FR as fetuses to be aborted. Would anyone truly take such actions? Would any parent knowingly consent to such a study? The Commission invested great

practice and policy, the Commission envisioned an ongoing EAB as a resource for local IRBs and for developing national policy on research ethics.[73]

Federal regulations on FR followed on July 29, 1975, and the moratorium on FR was lifted. Notably, these regulations (45 CFR Part 46, Subpart B) [74] have consistently reflected a higher commitment to the beneficence-based first point of the Commission on FR than any ever expressed by Congress. The regulations distinguish [75] between between research to "meet the health needs" of the fetus, and research to develop "important biomedical knowledge which cannot be obtained by other means." The standard

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hope in a future Ethics Advisory Board's role in these decisions on a case-by-case basis. (See footnote 6 above, at p. 67.) Indeed, some Commissioners said in debate on specific proposals that some important FR could not ethically be done without selectively assigning higher risks to fetuses to be aborted. The Commission's report was a compromise premised on strong hopes for the work of an EAB that functioned like a national IRB.

[73] On this third point, the Commission and those who support their legacy failed to reckon with the long-range task of creating a place for bioethics in government that truly protects a national resource like the EAB (or the Office for Protection from Research Risks, for that matter) from the effects of clashes with the various branches of government.

[74] including proposed rules to amend this Subpart, c.f. Federal Register (1998). 63 (no. 97), 27794-804, May 20.

[75] This distinction is a legacy of the Commission's use of the terms "therapeutic" and "non-therapeutic" research, towards which Robert Levine is so critical.

for research risks in the former case is "only to the minimum extent necessary to meet such needs" and in the latter case the standard is "minimal."[76] Knowing that there would be difficult cases of investigative FR with more than minimal risks, the Commission expected an EAB to review such protocols in FR (and for other areas) and make recommendations to the Secretary, DHEW, to whom the regulations gave authority to "waive" the minimal risk standard in FR.[77]

Following the elections of 1984 in which President Reagan was returned to office [composition of Congress?], Congress hotly

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[76] 45 CFR 46.208 (a). The regulations define "minimal risk" to mean.."that the probability and magnitude of harm or discomfort anticipated in the research are not greater in an of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 45 CFR 46. 102 (i). See my discussion of the history of the minimal risk standard in relation to Subpart B. Fletcher, J.C. (1993). Human fetal and embryo research: Lysenkoism in reverse - how and why? In Blank, R.H., Bonnicksen, A.L., (eds). Debates Over Medical Authority. New Challenges in Biomedical Experimentation vol. 2 (New York: Columbia University Press), 208-10.

[77] The Secretarial waiver was used only once by Joseph Califano, on the recommendation of the only Ethics Advisory Board, in 1979 for a study of fetoscopy in the context of hemoglobinopathies. Although the EAB requested that he approve this type of research as a category, he only approved the project itself. [Steinfels, M. (1979). At the EAB: same members, new ethical problems. Hastings Cent Rep 5,2. Secretary Patricia Harris allowed the EAB's charter to lapse in 1980 and there has never been another EAB, although federal regulations require that "one or more Ethical Advisory Boards shall be established by the Secretary." 45 CFR 46.204.

debated federal funding for FR and enacted legislation that is far more protectionist than the second point of the federal regulations. Public Law 99-158,[78] imposed the "Golden Rule" on all federally funded in utero FR, thus nullifying the "minimal risk" standard for the second category of FR.[79] This law effectively ended federal funding of any FR carrying any degree of risk [80] including research into normal fetal physiology that involved fetuses in the context of abortion. At this point in time, it is important to note the differences between federal law and federal

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[78] The Health Extension Act of 1985, November 20, 1985. For a good discussion of the legislative history of this Act, see Lehrman (footnote above, pp. 7-9). This Act also adopted a provision introduced by Sen. Gore in 1983 and established the Biomedical Ethics Advisory Commission (BEAC). The history of BEAC proves the hypothesis that since the National Commission, any national bioethics body solely created by and accountable only to Congress has a vanishingly small chance of success. For a discussion of BEAC's history, see Cook-Deegan, R. (1994). The Gene Wars. (New York: W.W. Norton), 256-62.

[79] "...the Secretary shall require that the risk standard (published in Section 46.102(g) of such Part 46 or any successor to such regulations) be the same for fetuses which are intended to be aborte and fetuses which are intended to be carried to term." Health Law Extension Act of 1985, Sec. 408 (b) (3).

[80] See: Fletcher J.C., Schulman J.D. (1985). Fetal research: the state of the question. Hastings Cent Rep 15, 6-12; Fletcher, J.C., Ryan K.J. (1987). Federal regulations for fetal research: a case for reform. Law, Med & Health Care 15(3), 126-38.

regulations on FR; the latter are less protectionist than the former.[81] The price of federal law on FR is described in Part III.

Federal Inaction on Infertility Research. Infertility is a significant public health problem and assisted reproductive technologies (ARTs) raise a wealth of complex ethical, social, and legal concerns.[82] Physicians define infertility as the inability to conceive after 12 months of unprotected intercourse or to carry a fetus to term.[83] Epidemiologists distinguish between primary and secondary infertility. Primary infertility is determined by the number of infertile couples with no children. Secondary infertility is becoming infertile after having one or more children. Using these categories, the National Center for Health

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[81] Those in charge of composing and redacting federal regulations to protect human subjects are aware of their role in protecting the legacy of the National Commission's commitment to FR because of its benefits. (William F. Dommel, personal communication, April 29, 1999) This protective role has been largely symbolic, because no investigative FR of any consequence has been funded. However, in any future reform of public policy on FR, the history of federal regulations and the original intent of the Commission ought to carry weight. The need to do limited and appropriate FR is even more important today that it was in 1974, if we are to have ethically and scientifically responsible fetal therapy.

[82] Amidst a very large literature, a very good recent review of these concerns is: The New York State Task Force on Life and the Law. (1998). Assisted Reproductive Technologies. Albany, NY: Health Education Services.

[83] Wymelenberg, S. for the Institute of Medicine (1990). Science and Babies. (Washington, DC: National Academy Press), 15.

Statistics estimated in 1988 that 2.3 million married couples were infertile. This translates into 8 percent (1 in 12) of the total number of all married couples in the United States.[84] The National Survey of Family Growth estimated in 1995 a slight drop in infertility to 2.1 million couples or 7.1 percent of 29.7 million married couples with wives of childbearing age.[85] Primary infertility among women has doubled due to the trend in large numbers of women deferring marriage and childbirth. [86]

Although primary prevention is the optimal approach to the public health problem, the major approach to treatment of infertility has been to combine fertility drugs with in vitro fertilization or other methods and sites to fertilize ova. The relative successes of assisted reproductive technologies (ART) has created a large industry and significant growth in infertility services.[87]

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[84] Ibid.

[85] Abma, J.C., et al. (1997). Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. Vital and Health Stat 23, 1. "However, even with the decreasing rate, the total number of infertile couples is the same as it was in 1982, because of the increasing number of married couples in the relevant age group." The New York State Task Force on Life and the Law. (1998). Assisted Reproductive Technologies. Albany, NY: Health Education Services, 11-12.

[86] New York State Task Force, see footnote 75, 12.

[87] OTA reported that from 1983 to 1987, the number of infertility centers offering IVF grew from 10 to 167. U.S. Congress, Office of Technology Assessment, (1988). Infertility.

The concern in this section how a pattern of federal inaction regarding infertility research illuminates the background of the ban on FFER. This story mainly concerns research on the safety and efficacy of IVF. A de facto moratorium was placed on federal funding of IVF in 1974 (along with FR) until an Ethics Advisory Board could make recommendations to the Secretary, DHEW. In May 1978, the EAB reviewed a proposal from Vanderbilt University received by the NIH in 1977 and approved by a study section. An EAB was chartered in 1977 and convened in 1978. In May 1979, the EAB recommended approval [88] for federal funding on safety and efficacy of IVF and embryo transfer in the treatment of infertility. The approval was also for study of spare, untransferred embryos, provided researchers had IRB approval and the informed consent of women who would receive any transferred but studied embryos. The EAB set a 14-day cutoff for studying embryos in vitro on condition that gametes be obtained only from lawfully married couples. Richard McCormick, also then an EAB member, participated in this compromise. He departed from a Vatican position against any

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Medical and Social Choices. OTA-BA-358 (Washington, DC: U.S. Government Printing Office, May), 157. The role of the Serono Corporation and other commercial enterprises in this growth industry is described in Hotz, R.L. (1991). Designs on Life. New York: Pocket Books, 176-203.

[88] See footnote 7 above, p. 3.

technologically assisted pregnancies, even in lawfully married couples. This position was later promulgated as moral dogma.[89] Secretary Califano published the EAB's report for public discussion but resigned at President Carter's request in late September 1979. No Secretary of HEW or HHS has approved the EAB's recommendations. No federal support of IVF, except with animals, has ever been permitted. Two causes contribute to this pattern of reluctance: a view of infertility as a condition non-deserving of government support in research, and moral concern to avoid using embryos in research.[90]

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[89] Congregation of the Doctrine of the Faith. (1987). Instruction on Respect for Human Life in its Origin and on the Dignity of Procreation: Replies to Certain Questions of the Day. Vatican City: The Congregation.

[90] Two examples are provided. Patricia Harris, Secretary, DHEW wrote in her own hand in response to a decision memo (Harris, 1979, Memorandum: to Kathy Schroeher, Executive Secretariat, DHEW, November 26) on the 1979 recommendations of the Ethics Advisory Board to support IVF research: "I need greater justification for such research. Whether the research will take place with our without government support is not really relevant. Why should government support such an area as this! I have read the material. It is not persuasive." Harris mainly saw IVF as a procedure for the advantaged.

Secondly, in 1988, the Office of Technology Assessment reported to Congress: "The effect of this moratorium on Federal funding of IVF research has been to eliminate the most direct line of authority by which the Federal Government can influence the development of embryo research and infertility treatment so as to avoid unacceptable practices or inappropriate uses. It has also dramatically affected the financial ability of American researchers to pursue improvements in IVF and the development of new

HEW Secretary Patricia Harris allowed the EAB to lapse on September 30, 1980, when its charter and funding expired. One view [91] is that she did so to avoid overlap with the President's Commission, which was planned to succeed the National Commission. Congress had created the President's Commission largely to study ethical problems in medicine, but by 1980 had not yet appropriated funds for operations. However, Ms. Harris dispanded the EAB fully aware that it was the only lawful body that could recommend "waiver" of minimal risk in research. NIH Directors in the 1980s appealed to various Secretaries of HHS to recharter the EAB and approved its recommendations for IVF research. No action was taken until, under pressure from Congress, Dr. Robert Windom, Assistant Secretary for Health, announced on July 14, 1988 that a new charter for an EAB as to be drafted and discussed in public, and a new EAB

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infertility treatments, possibly affecting in turn the development of new contraceptives based on improved understanding of the process of fertilization." U.S. Congress, Office of Technology Assessment, (1988). Infertility. Medical and Social Choices. OTA-BA-358 (Washington, DC: U.S. Government Printing Office, May), p. 179.

For more discussion of the ethical and political implictions of this pattern of federal reluctance, see also: Blank, R.H., (1997). Assisted reproduction and reproductive rights: the case of in vitro fertilization. Pol & the Life Sci 16, 279-288;.

[91] Norman, C. (1988). IVF moratorium to end? Science 241, 405.

appointed.[92] A draft of a charter was published in the Federal Register and comments invited, but no approval was given before the transition to the Bush Administration, which never acted on the issue. As stated above, following the elections of 1993, Congress nullified the EAB requirement for IVF research, but no NIH funding of research involving human embryos in this context occurred.

Then Congressman and now Senator Ron Wyden (D-OR) has been the main champion of federal involvement in infertility research. While in the House, Wyden held hearings on consumer protection issues involving IVF clinics.[93] Long concerned with the issue of regulating ART programs, the only federal leverage available has been in the wake of the Clinical Laboratories Act (CLIA), which regulates a wide range of laboratory procedures.[94] Due to Sen. Wyden's efforts, the 1992 Fertility Clinic Success Rate and Prevention Act requires the Centers for Disease Control and Prevention (CDC) to develop model standards for state certification

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[92] Ibid.

[93] Wyden, R. (1989) Opening remarks and testimony at the Hearing on Consumer Protection Issues involving In Vitro Fertilization Clinics, before the House Subcommittee on Regulation, Business Opportunities, and Energy. Washington, D.C., Mar. 9.

[94] 42 U.S.C.A. ¶ 263a (1997). CLIA is discussed in the New York State Task Force Report, see footnote 73 above, p. 410.

of embryo laboratories.[95] The standards concern issues of performance of procedures, quality control, records maintenance, and qualifications of employees. However, the law states that the standards do not regulate the practice of medicine in ART programs. Aside from the laboratories in which embryos are generated for IVF, the entire spectrum of infertility services and the research that is conducted within these centers is unregulated except by the canons of professional ethics.

Federal Regulation and Law on Fetal Tissue Transplant Research (FTTR).

In 1986 neurosurgeons at the NIH's Clinical Center designed a study to give Parkinsonian patients the choice of an adrenal autotransplant or a fetal neural cell transplant. After approval of the project by an IRB, Dr. James Wyngaarden, NIH director, decided in October 1987 to seek higher review of FTTR by the assistant secretary of Health. In March 1988 (there being no EAB), Dr. Windom withheld approval, placed a moratorium on FTTR, and asked that the NIH convene an advisory pane to consider a list of ten

[95] 42 U.S.C.A. ¶ 263a-1 et seq. (1997).

questions. His main concern was that the benefits of FTTR would induce women ambivalent about abortion to have one.

The NIH assembled a 21-member panel, and in December 1988 the panel approved a report [96] by a vote of 18-3 recommending federal funding of FTTR. As noted above, the majority argued that the use of fetal tissue to treat disease was separable from the morality of abortion. The reasoning of the panel was that FTTR was a type of cadaveric transplantation.[97] Three panel members with conservative theological views dissented due to FTTR's association with abortion. The panel shaped twelve recommendations to oversee and guide FTTR in the hope that these would become federal regulations.

The NIH panel report, submitted to the director of the NIH and approved unanimously by his advisory council, was rejected by letter [98] without any public hearings or prior notification published in the Federal Register. Acting unilaterally and in violation of the understandings that had created the EAB, Secretary Sullivan continued the moratorium "indefinitely." He gave as his major reason that the Bush Administration and Congress opposed any funding of activities by HHS that "encourage or promote abortion."

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[96] See footnote 6 above.

[97] Childress, J.F. (1991). Ethics, public policy, and human fetal tissue transplantation. Kennedy Inst of Ethics J, 1, 93-121.

[98] Sullivan, L.B. to William F. Raub. November 2, 1989.

The press[99] and a letter from Rep. Theodore Weiss to Dr. Sullivan[100] cited a memorandum from Richard Riseberg, HHS counsel,saying that the extension of the moratorium was on a "shaky legal base" and could be actionable as a violation of federal law[101] requiring that such decisions be published in the Federal Register and made the subject of rulemaking.[102]

In 1990 Rep. Henry Waxman (D-CA) introduced the Research Freedom Act (H.R. 2507) to overturn the moratorium on FTTR. The full law, as subsequently passed by Congress in 1993 after a long struggle, restrains the secretary of HHS from imposing a ban or moratorium on research for ethical reasons without the concurrence of an EAB convened to answer that question and establishes an authority within current law for federal support of FTTR.[103] The

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[99] Hilts, P.J. (1990). U.S. aides s shaky legal basis for ban on fetal tissue research. New York Times, Jan. 30, A-1.

[100] Weiss, T. to Sullivan, L., January 26, 1990.

[101]

[102] The term "indefinite" was chosen to circumvent federal law and deflect legal action against HHS. A document leaked from the Public Health Service to the press was cited by Hilts (see footnote 96 above, at A-1): "We have chosen to make the moratorium indefinite rather than permanent, because a permanent prohibition of this research would require formal rulemaking and this would require extensive public comment and would be rather easily susceptible to litigation which could reverse this action."

[103] See footnote 57 above.

other provisions of the law relevant to the consent process and other safeguards will be described in Part II under Case 1.

Ban on Federal Funding for Embryo Research.

From an ethical perspective of beneficence and utility, the NIH Human Embryo Panel's Report in 1994 [104] made a strong case for federal funding of embryo research. Before the ban was passed, the threat of strong opposition from Congress towards any embryo research inhibited NIH approval for funding several clinically relevant projects that passed NIH scientific review in 1994 [105] concerned with cancer, genetic research, infertility, and contraceptives. The Human Embryo Research Panel specifically recommended these lines of research.[106] After the ban, the NIH received no proposals involving embryo research. Part III discusses the costs of forgoing NIH involvement and scientific peer review in these areas.

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[104] See footnote 7.

[105] Although the NIH could have funded research with donated excess embryos in 1994 in the interim between President Clinton's decision not to support NIH funding of creation of research embryos and the imposition of the ban, "As of spring 1995, NIH has yet to fund any human embryo research, despite 70 pending proposals and eight proposals that have cleared scientific review." Charo, R.A. (1995). The hunting of the snark: the moral status of embryos, right-to-lifers, and third world women. Stanford Law & Policy Rev 6, 11-27.

[106] See footnote 7, pp. 7-8.

This historical review has hopefully provided background on why the ban on FFER continues a public policy [107] that embryos, like fetuses, deserve virtually absolute societal protection from destruction or harm in research activities. The language of the embryo ban is framed exactly in terms of federal law restricting funding for fetal research. [108] Readers should also recall that Congress acted to deny federal funding (with exceptions) for elective abortions in the Medicaid program.[109] In a democracy, the moral beliefs of the elected majority can prevail when it acts to deny federal funding for activities it views as ethically unjustified. Federal and state government may use denial of funding to ameliorate the divisiveness of intractable moral disputes like abortion. Such actions are understandable in a nation with divided (public and private) systems of health care and research.

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[107] This view will be discussed more fully below and in the Appendix.

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

[109] First introduced in 1976, the Hyde Amendment, named for its sponsor, Henry Hyde (R.-Il), restricts funding for the federal share of Medicaid only to cases where two physicians attest that continuation of the pregnancy will result in severe and lo lasting damage to the woman's physical health, and in cases of reported rape and incest. The law took effect after a Supreme Court ruling: *Harris v. McRae* 448 U.S. 297 (1980).

Do such laws violate scientific freedom? Denial of funding does not legally violate scientists' freedom of inquiry, although poorly justified legislative and executive actions clearly infringe on the values that underlie scientific and academic freedom. Any proposition that scientific freedom is constitutionally protected is highly debatable. In my view, Robertson clarified the constitutional question of denial of funding long ago:

> The [scientist's] freedom to select the means [of inquiry and research] may refer to the freedom to think, to read, to write, and to communicate, the freedom to observe events or interactions, or the freedom to experiment. Freedom of inquiry in any of these senses does not, however, include a claim that the government must fund any particular activity designed to advance knowledge.[110]

Signs of Change. As noted above, change has begun in federal science policy and the interpretation of the embryo ban. Harriet S. Rabb, General Counsel, DHHS, ruled that the NIH could legally fund uses of PSC research but not activities deriving PSCs from embryos.[111] Assuming that Congress allows the Rabb ruling to stand,

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[110] Robertson, J.A. (1978). The scientist's right to research: a constitutional analysis. South Cal Law Rev 51, 1203-79.

[111] See footnote 22 above. Rabb based her opinion on a scientific definition of PSCs as neither a human "organism" as defined by the statute nor capable of developing 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 companies or universities funding such work, if the equipment and laboratory facilities are not purchased

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

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or operated with federal funds.

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 (From Jay Dickey, et al. to Donna Shalala, Feb. 11, 1999) 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 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 on fetal research [45 Code of Federal Regulations ¶46. 206 (3)] and law on fetal tissue transplant research. [Public Law 103-43, ¶112 (c) (4).] The effort is 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. One does not have to agree with their premises to agree with the point that the morality of access to embryos cannot be separated from the morality of uses of PSCs.

Secretary Shalala answered (Letter. From Donna Shalala to Jay Dickey, et al., Feb. 23, 1999) 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."

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

## PART II. AN INCREMENTAL APPROACH TO NBAC'S TASKS

### A. The Tasks of NBAC

Table 3 shows NBAC's four tasks in regard to ethical and public policy issues in PSC research:

Table 3. 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 -- on access and 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.

Doing an exhaustive review is problematic beyond Cases 1 and 2. No scientific information exists to use in evaluating Case 3. Cloning somatic cells does produce viable embryos in animals.

Cloning somatic cells to produce a sheep [112] as well as mice and cattle [113] has been done. Fusing adult mouse cells with enucleated mouse oocytes, followed by implantation and reproduction, has also been done.[114] However, despite the obvious clinical benefits envisioned in Case 3, deriving PSCs from cloned embryos has not even been done in mice.[115] In 1984, The Council for Science and Society in the United Kingdom formulated a working rule for ethical debate on new technologies:

> ..refrain from moral judgment unverifiable possibilities -- as notational cases rooted neither in the reality of experience nor in a specific context.[116]

This oft-broken rule is relevant to NBAC's tasks with Case 3. Also, other groups[117] are now studying intentional and unintentional

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[112] Wilmut, I., Schnieke, A.E., Kind, A.J., Campbell, K.H.S., (1997). Viable offspring derived from fetal and ault mammalian cellss. Nature, 385, 810-13.

[113] Wilmut, I. "Cloning for Medicine" Scientific American, Dec. 1998.

[114] Wakayama, T., Perry, A.C.F., Zuccotti, M. (1998). Full-term develelpment of mice from enucleated oocytes injected with cumulus cell nuclei. Nature, 394, 369-73. Obtaining PSCs from embryos that resulted from fusion of adult cells with enucleated human oocytes could become a Case 5.

[115] See footnote 17 above.

[116] Council for Science and Society. Human Procreation. (1984) Oxford: Oxford University Press, p. 7.

[117] A Task Force of the American Association for the Advancement of Science (AAAS) is studying the ethical, legal, and

germline gene tranfer, one of the subjects of Parens' challenge to NBAC. 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 discusses an incremental or case-by-case approach to NBAC's tasks. Familiarity with this approach in science, ethics, and law is a strength. When presented with several morally problematic cases which appear to be similar, one proceeds incrementally, or case-by-case. Rather than beginning from first principles and working down or across, one begins with a case, asking: "What is morally at stake here?" In response to this question, the principles and moral rules linked to the case can be discerned and would also be discussed in extant literature about the case. 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 moral deliberation.[118]

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social issues in intentional germ-line gene transfer; the NIH-RAC is presently examining unintentional germ-line effects of somatic cell gene therapy.

[118] A discussion of the key elements in such an approach that focuses on clinical cases is in: Fletcher, J.C., Lombardo, P.A.,

Comparing and contrasting moral similarities and differences among cases is both a descriptive and evaluative task of this approach. 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 sees such clear differences between cases as to create a new branch or line of cases.

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. Among methodologies in ethics, this approach is known as casuistical reasoning.[119] After

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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.

[119] 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

considering its weaknesses, the remainder of this part illustrates its use 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." [120] A case-by-case approach is bound to be less certain about the right account of morality than about moral fallibility. The point is that modesty about the place of ethical theory or systematization invites criticism.

Those with sharply divergent views on fetal and embryo research will also disagree with this approach. John Harris [121] 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

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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.

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

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

this purpose." (p. 45) 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 about, not simply what we are hoping for.." (p. 46)

A view that human embryos and fetuses deserve vigorous protection from research -- due to moral status as persons or potential persons -- will not concede the moral acceptability of any of the four cases. This view would hold that an incremental approach is fatally compromised because it begins from a wrong premise 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 to 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."[122] Deriving PSCs from fetal tissue after

[122] Subsequently embodied in the NIH Revitalization Act of 1993.

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-based Considerations. Although open to challenge, a sufficient moral consensus emerged and has persisted through several sessions of Congress that society ought not to forgo the biomedical knowledge and/or therapeutic benefits to patients of research on transplants with fetal tissue obtained after elective abortions. A consequentialist argument strengthens the obligations of beneficence in Case 1. Namely, society and science ought not to forgo the uses of fetal tissue, especially since it would otherwise be discarded. Most of the consequences of allowing viable fetal tissue to go to waste are bad. This option would respect the moral views of opponents of abortion, but all of the parties who could benefit from research will lose if the opportunity is forgone. Uses of fetal tissue in transplant research are sometimes good for patients but almost always good for science.

The moral consensus that prevails about access to aborted fetuses to obtain fetal tissue is properly framed in negative rather than positive terms. The consensus is not that society

should vigorously pursue access to aborted fetuses. Rather, it is that no overriding reasons compel society to forgo benefits from fetal tissue research to patients and science. The evolution of the morality of fetal tissue transplant research in this society contributes to the assurance with which NBAC can be confident that Case 1 is the most settled case for PSC research. If the arguments that condemned the research uses of fetal tissue because of association with elective abortion[123] had prevailed and dominated the moral consensus that emerged, very different moral principles and rules would be embedded in Case 1. This outcome did not occur. The moral debate about research uses of fetal tissue led to a consensus composed of elements drawn from arguments on both sides of the issue. The consensus permitted limited research involving fetal tissue with safeguards that protected society's interests in upholding a principle of respect for the intrinsic value of life and discouraging abortion when there is a reasonable alternative. These various concerns were specified and expressed through a law that permitted federal funding and defined the current public process for regulating fetal tissue transplant research.

b) Respect for autonomy. Although some contest it, there is a sufficient moral consensus that society ought to respect the

[123] cite Burtchaell, etc.

autonomous choices to donate fetal tissue for research of women 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.[124] 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-based Considerations. 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

[124] 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.

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.

NBAC's review of Case 1 needs to cover the report of the Human Fetal Tissue Transplantation Research Panel,[125] the history of the "indefinite" moratorium,[126] 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, which has proceeded entirely within the federal requirements and without significant incident.[127]

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[125] See footnote 6.

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

[127] 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.

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 the literature in the 1990s on the complicity issue.[128]

Case 2. Case 2 is similar to Case 1 in three morally important ways and 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. However, use must be further specified to the preimplantation stage, and further, that uses 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.[129] Given research findings in the

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[128] See Siegel, A. (1999). Complicity and Consent (draft). NBAC Document, April 8, 1999.

[129] 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.

mouse, it appears likely that human beings will receive benefits from PSC research.[130] The Human Embryo Panel supported federal funding of derivation of PSCs from embryos in 1994. Today, science and society are in verifiable proximity to this goal. Advances in PSC research, stem cell biology, and cloning technology are the major new factors in the scientific context.

lack of evidence that embryo research had yielded clinical benefits was among several criticisms of the NIH Embryo Panel's position. Daniel Callahan [131] 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

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[130] 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.

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

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 the inevitability of discard. Whereas all fetal tissue is discarded if not made available for research, only a certain percentage of embryos will be eventually discarded.[132] The options for couples in IVF about disposition of excess embryos are: cryopreservation for subsequent thawing and use to treat their infertility, donation to other infertile couples, or for research.[133] The same consequentialist reasoning about inevitable discard used in Case 1 also applies to Case 2 and heightens the

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[132] 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 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.

[133] 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.

obligation to be beneficent.[134] Reasons for patients and society to forgo such benefits must be strong enough to be overriding.

In this vein, 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."[135]

NBAC can use this classic statement of the moral limits of biomedical research with human subjects as a baseline from which to evaluate the moral effects of embryo research. [136] What work does the statement do in relation to Case 2? Jonas' query will be explored below in a section on considerations of non-maleficence.

We have seen so far that beneficence-based arguments heightened by the consequences of inevitable discard and loss of

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[134] Parens' focuses on the problems of ascertaining the "intentions of embryo makers" at the time of creation of embryos (i.e., to reproduce or to use for research) and is skeptical about the validity of a morally relevant difference between Cases 2 and 4. However, Parens does not take account of the similarities of Cases 1 and 2 in terms of the consequences of discarding fetal or embryonic tissue. Parens, E. (1999). What Has the President Asked of NBAC? (draft). NBAC Document, April 4, pp. 10-13.

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

[136] 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.

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 some state bans on IVF embryo research implicitly forbid embryo donation for research. These bans conflict with a right to make such donations in that is

respected in other states in the context of privately supported research.

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. Case 1 and Case 2 differ in one significant respect, i.e., the fetus as a source of PSCs is dead and cannot be harmed by research activities, but 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 that the abortion causes the death of the fetus, and the research causes the death of the embryo. How ought this difference be morally evaluated? Is Case 2 comparable in any way with cases of transplanting organs from the "dying but not yet dead" to benefit others and society, e.g., the case of harvesting organs from dying anencephalics prior to brain death?

Answers to these questions depend upon answers to deeper questions about moral perspective. What kind or type of case is Case 2? What are the strengths and weaknesses of varying perspectives on the moral worth of embryos? Can embryos even be "harmed" in research? 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-replacement therapy "not worth having?"

What kind of case is Case 2? If viable PSCs were derivable from donated embryos that were "allowed to die," [137] then Case 2 would clearly follow Case 1 in a line of cases of cadaveric sources of organs and tissues, including fetal tissue. Cadaveric transplants 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, given the procreative intent[138] of infertile couples and the clinicians who help them,[139] Case 2 is also not a case of

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[137] Two experts, Ted Thomas (University of Virginia) and Mark Hughes (Wayne State University), were asked their opinion on the question of whether viable PSCs would survive embryo death. Each viewed it as highly improbable but knew of no research on the specific question. Dr. Hughes referred to the non-viability of DNA samples taken from 4-5 day old embryos in the process of dying. (Personal communication, Feb. 25, 1999)

[138] The moral relevance of parental intent to procreate as well as their active concerns for their embryos is discussed in: Annas, G.J., Caplan, A., Elias, S. (1996). The politics of hman embryo research - avoiding ethical gridlock. N Engl J Med 334, 1329-32.

[139] Parens' points about the difficulties of oversight bodies in discernining intentions of "embryo makers" are well taken. See footnote 100 above, p. 11. However, oversight bodies ought to be

creating embryos solely for research as are Cases 3 and 4. Cases 3 and 4 are in a new line of embryo cases posing an issue of 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.

In my view, if the donative feature and the inevitability of discard in Case 2 can be authenticated, then Case 2 is more similar to Case 1 than Cases 3 or 4. The similarity is especially strong when one considers the largely bad consequences of discarding fetal and embryonic tissue suitable for research. Moral authentication of donation and discard requires two stages of the informed consent process. The first stage would be informed consent for treatment of infertility by the procedure of IVF. Patients need to understand IVF's known risks and benefits. This first discussion should include the issue of the number of viable embryos to be transferred.

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more concerned with the authenticity of the consent process for parents to donate embryos for research than with discerning their intentions.

The treatment stage ought to be separated from a second stage of informed consent regarding cryopreservation and options for disposition of excess embryos: i.e., continued treatment of the couple's infertility, donation to other infertile couples, and donation for research. The decision to donate embryos for research should be the last option explained with no undue influence on the choice of the couple or the woman.

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 lose their moral worth because they have been selected for research? [140] If one views embryos as having no moral standing at all, then the "moral worth" question is moot. If one has serious moral concerns about Case 4 on the grounds that "it seems to cheapen the act of procreation and turn embryos into

[140] This is a complex question that is related to the issue of moral worth of fetuses 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 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 ought to be no differences between the moral worth of embryos, regardless of their source. This policy framework is open to challenge, but it is the prevailing framework.

commodities,"[141] then one will focus strongly on the donative feature and the integrity of the consent process. Research with embryos donated by parents is easier to justify than creating embryos for research, because the parents have authority over the disposition of their embryos. [142]

The Appendix discusses 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).[143] The Panel desired to

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

[142] In my view, the decisive factors in Cases 3 and 4 combine the degree of weight given to the moral status of embryos with proximity to scientific and clinical benefits.

[143] The Human Embryo Panel's choice of a "pluralistic" ethical analysis of the moral status of embryos reveals a degree of equivocation in its Chairman's statements in his letter of transmittal to the Advisory Committee to the Director, NIH. Dr. Muller states: "The panel began from the position that it was not called upon to decide which among the wide range of views held by American citizens on the moral status of preimplantation embryos is correct, but rather that its task was to make recommendations that would assist the NIH in developing guidelines for preimplantation human embryo research that took full account of generally-held public views regarding the beginning and development of human life." Stephen Muller to Ruth Kirschstein, see footnote 7 above, p. v. The report describes two approaches to debates on the issue of moral status: one proposes some single criterion, a second approach is "pluralistic." "It sees moral respect and personhood as deriving not from one or even two criteria from from a variety of different

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 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. [144]

The Panel cited similar reasoning about the ethics of embryo research by the U.S. Ethics Advisory Board in 1979, the Warnock Committee in the U.K. in 1984, and a Canadian commission in 1993.

In an important article, Annas, Caplan, and Elias criticized the Panel's ethical perspective. [145] These authors found that:

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and interacting criteria." See footnote 7 above, at pp. 35-36. A fair reading of the report would lead one to conclude that the Panel took a definitely liberal position on moral status, did not defend it as such, and then used the term "pluralistic" as a surrogate for what the liberal majority might approve.

[144] See footnote 4, pp. 38-39.

[145] At footnote 63.

> "the pluralistic framework.. is not convincing. This is so primarily because that framework requires a detailed analysis that explains why the particular properties cited confer moral worth, or to what degree each property cited is necessary and sufficient. Without such an underlying rationale, the framework looks like an attempt to rationalize a desired conclusion -- namely, that some research on embryos ought to be permitted -- rather than to derive a conclusion from an ethical analysis. (p. 1330)

Beyond critique of the argument's content, the article was very critical of the Panel's discussion of the moral status of the fetus apart from the relationship of parents with their embryos or an intent to procreate. They argued that "..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 their view, the moral standing of embryos not only derives from a "cluster of properties" that the embryo possesses but also from the "interests that potential parents and society bring to procreation and reproduction.."[146] This criticism revealed the need for a moral framework for embryo research that compensates for the weaknesses of the work of the Human Embryo Panel and draws on other ethical perspectives. NBAC's report on PSC research should aim for improved arguments. Part III of this paper undertakes this task.

Can Embryos Be Harmed in Research? The article by Annas, et al. makes the excellent point that the interests of parents and

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[146] at footnote 63, p. 1131.

society in procreation can be damaged by morally unjustified embryo research. But can an embryo be harmed in research? On the one hand, one may concur with the Ethics Advisory Board's [147] position of "profound respect" for the preimplantation human embryo, due to its human origins. On the other hand, one can hold without contradiction that an experiment ending in an unimplanted embryo's death did not "harm" the embryo. The embryo is an organism with human origins but without sentience or 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 a clear and "bright line" difference emerges between the moral status of living children and embryos. To be sure, society does not permit comparable experiments with living children who are sentient and who have interests. However, society does permit Phase I trials in children with cancer, and these trials carry a risk of morbidity and mortality.[148]

It is possible, of course, to damage an embryo in research. The damage would become "harmful" in the moral sense only if the

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

[148] Furman, W.L., Pratt, C.B., Rivera, G.K. (1989). Mortality in pediatric phase I clinical trials. J Nat Cancer Inst 81, 1193-94.

embryo was transferred to a human uterus and a future sentient person was harmed by the damage once done to the embryo.[149] This potential abuse can be prevented by regulation forbidding the transfer to a human uterus, after research activities, of any embryo or its equivalent.

Jonas' query. Embryo research has proceeded in the private sector, regulated only by professional ethics. In this context, a wide diversity of practices could probably be found among researchers located in the nation's infertility centers.[150] Until more is known about the actual shape of these practices, it is difficult to answer Jonas' query in terms of whether these unregulated activities are "too ruthless a pursuit of scientific progress." One can cite damage done by lack of regulation and accountability to "society's moral values", but it is debatable whether embryo research as conducted today in the private sector is seriously "eroding" those moral values. In my view, if limited to

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[149] 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.

[150] What is known about these practices? Has any research been done about whether the guidelines for embryo research recommended by the American Society for Fertility and Sterility are followed? Is it known whether researchers supported by private funds submit their protocols to local IRBs?

Case 2 and under conditions discused in Part III, FFER could proceed incrementally. [151] Part III provides a moral argument to support this step. It is obvious, however, that a too "ruthless" or commercially aggressive pursuit of embryo research could seriously threaten the values defended by Annas, et al. and others. For example, if researchers -- without any public discussion -- abruptly pursued a version of Case 3 by fusing human somatic cells with enucleated animal ova to create defective embryos in order to derive PSCs, the Jonas query could clearly be answered in the positive. The deliberate and cautious approach to PSC research taken by the NIH to PSC research is ethically appropriate and commendable.

Other Concerns Based in Nonmaleficence. The Human Embryo Research Panel carefully outlined a set of principles and guidelines[152] 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

[151] This step could be taken after the NIH's "downstream" approach to funding PSC research has had a chance to be tested.

[152] 1994, vol 1, pp. x-xi.

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) a 14-day limit on length of research.

Case 3. This case involves PSCs to be derived from human (or hybrid) embryos generated asexually by SCNT, using enucleated human or animal ova for fusion. The rule of the Council on Science and Society is relevant to Case 3. [153] Until more is known about this unverified possibility, moral judgments are inappropriate. Unlike Cases 1 and 2, virtually nothing is known scientifically about SCNT as a source of human PSCs. Case 3 is ranked above Case 4 due to the therapeutic potential of growing the patient's own cells to return to the patient in autologous cell-replacement therapy, in theory avoiding graft vs. host disease. Considering the prospective clinical benefits of SCNT-created PSCs, more moral support for Case 3 than for Case 4 seems predictable. A balancing and controversial factor is that the product of SCNT (using an enucleated human egg) would arguably be a human embryo which could become a human being if transferred to a uterus. The NBAC's

[153] See footnote 113 above.

recommendations for a ban (with sunset provision) on cloning a human being are relevant here.[154] 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?[155] 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

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[154] Cite cloning report.

[155] Julian Savulescu sees no morally relevant differences between "a mature skin cell, the totipotent stem cell derived from it, and a fertilized egg. They are all cells which could give rise to a person if certain conditions obtained." Savulescu, J. (1999). Should we clone human beings? Cloning as a source of tissue for transplantation. J Med Ethics 25, 87-95. I am inclined to agree with this reasoning, although the verifiable possibilities of creating implantable human embryos by cloning must still be established.

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, the main point is that to go throughly down the SCNT road requires a full scale review that will be only speculative due to lack of information.

Considering the intent of the progenitors, Case 3 is more similar to Case 4 than it is to cases 1 and 2. The intent is to create embryos by SCNT only for the sake of research.

Case 4. In this case PSCs would be derived from human "research" embryos created from donor gametes. Although the activity is the same in Case 4 as in Cases 2 and 3 -- 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. Depending on the circumstances, the donors may be individuals unknown to one another, or couples with particular genotypes of interest to researchers. 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 for inheritable genetic modifications of embryos.[156] The embryos would be belong to couples at high risk for genetic disease. NBAC does not have the time or resources at present to conduct a full exploration of this topic.

In addition to their major arguments in support of FFER, 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. [157]

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[156] Also inappropriately called "human germline gene therapy." This intervention should not be called "therapy" because there is individual who is the object of therapy. Eric Juengst views this intervention as treatment of the embryo's DNA and prevention of disease in the future child. One should also not use the term "therapy" in connection with an unproven technique.

[157] Gearhart, Science 6 Nov 1998, 1061

The discussion has shown important differences between Cases 1-2 and 3-4. Also, 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.

Transition to Part III. Hopefully, Part II has presented persuasive reasons why an incremental approach to NBAC's tasks is preferable to an exhaustive approach. Also, the principles and rules embedded in Cases 1 and 2 can serve as sources of appeal to strengthen the case for consensus among Commissioners as to why these are defensible situations for access to fetuses and excess embryos for PSC research. However, a fuller moral argument is necessary to justify federal funding for access to embryos in Case 2. Let us now turn to that argument.

## PART III. MORAL ARGUMENTS FOR FEDERAL FUNDING OF RESEARCH INVOLVING EXCESS EMBRYOS

### A. IVF, Embryo Research, and Public Bioethics

Before in vitro fertilization (IVF), the only purpose to generate embryos was procreation, i.e., to produce offspring. IVF added a second purpose: to view the preimplantation embryo and study a variety of biological and clinically relevant questions. Before IVF, gynecological surgery [158] was the sole means to view the preimplantation embryo or to obtain specimens. Rock and Menkin (1944), Edwards, et al. (1969), and Soupart and Strong (1974) pioneered IVF.[159] IVF provided a window of unparalleled opportunity but one clouded with moral controversy. From the outset, moral traditions that value only "natural" human reproduction challenged the moral justification for IVF and embryo research.

Embryo research has a variety of goals, i.e., to improve infertility treatment, to understand the preimplantation stages of the human embryo, to study origins of some types of cancers, genetic disorders, birth defects, etc. When DNA technology and IVA

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[158] Dr. John Biggers informed the Ethics Advisory Board in 1979 that, prior to IVF, the total body of information about human ova and embryos was comprised of 15 specimens in the world's literature. Ethics Advisory Board, Appendix, No. 8, pp. 7-18. Discussed in Grobstein, C. From Chance to Purpose (Reading, MA: Addison-Wesley, 1981), p. 36.

[159] Van Blerkom, J. (1994). The history, current status, and future direction of research involving human embryos. In National Institutes of Health. Papers Commissioned for the Human Embryo Research Panel. (1994) vol. 2, p. 9.

converged, scientists could pose basic questions: e.g., "When does gene expression begin in the embryo?" [160] Studies of such questions are permitted in the U.S. private sector but banned in the federal sector.

Embryo research is a major step in moral evolution. Indeed, there is not only a long-standing moral debate about creating embryos for research by fertilizing ova with sperm but a new phase of that debate about asexual creation of embryos by SCNT. One should expect a certain degree of confusion and a great need for education among the public about these matters.[161] The evolution of

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[160] Braude, P., Bolton, V., and Moore, S. (1988). Human gene expression first occurs between the four-and eight-cell stages of preimplantation development. Nature, 332, 459.

[161] Although she agreed in principle with the Human Embryo Panel's recommendation to approve federal funding for creating embryos only for research, Patricia King's partial dissent to the Human Embryo Panel's report stated: " Allowing fertilization of oocytes expressly for research purposes offers potential for benefit to humankind, but it also raises fundamental ethical concerns. The prospect that humanity might assume control of life creation is unsettling and provokes great anxiety. The fertilization of human oocytes for research purposes is unnerving because human life is being created solely for human use. I do not believe that this society has developed the conceptual frameworks necessary to guide us down this slope. My concerns are heightened in the context of research activities where practices cannot be monitored easily by the public and where it is difficult to ascertain whether the research is being conducted responsibly." See footnote 7 above, NIH Human Embryo Panel Report, vol. 1, p. A-3. Given the strong reactions to the Panel's report, Prof. King's dissent was correct. A more moderate and incremental approach could

moral beliefs guiding social roles, practices, and institutions occurs very slowly. [162] Conflicts of loyalties and intense struggles, which are not always peaceful, mark the paths of such changes.[163] In open democracies, an electorate and a judiciary informed by different moral traditions help to guide the scope and pace of moral evolution.

Furthermore, national and state commissions in bioethics can play a key role in providing guidance to policy makers and the public on controversial moral issues in research and medicine. [164]

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have been taken by the Panel. Her words are just as fittng today as in 1994 and should serve as a caution to NBAC.

[162] The Warnock Commission (1984) in the U.K. was the first public bioethics body to address the questions of embryo research. Their report eventually led to the an Embryo Research Act (1990) which permitted embryo research under the careful scrutiny of a public authority that grants licenses for this activity. See, Department of Health and Social Security, (1984). Report of the committee of inquiry into human fertilization. London: Her Majesty's Stationery Office, 1987.

[163] Rachaels, J. (1990). Created From Animals, (New York, Oxford University Press) is 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.

[164] Cite the OTA study (1990?) on the history and various types of commissions and panels in biomedical ethics in the federal sector. Also see: 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.

Insofar as PSC research is concerned, NBAC can contribute to present and future federal and state policy on the practice of human embryo research. Key questions are: Is it morally acceptable to use *any* embryo in research? Is there a morally relevant difference between embryos donated by infertile couples and embryos made by scientists but intended only for research? To what degree should society protect human embryos in research? [165] Answers to these questions draw on moral and political traditions, as well as policies governing the relation of science and society. The next section previews the main argument in this paper.

B. Conflicting Moral Views and a Third Possibility

Technology does not cause the moral problems linked to IVF and embryo research. Clashing interpretations of the moral legitimacy of using and discarding creating embryos for research give rise to these problems. PSC research today is mainly embroiled in renewed

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

controversy about the moral legitimacy of using live embryos in research.[166]

Two polar opposite positions appeal to the same ethical principle -- respect for persons-- but totally disagree on what ought to be done. These positions focus almost solely on the moral status of the human embryo. Each view appeals to biological data to settle the issue. Defenders of the first position argue that "..the human being must be respected -- as a person -- from the very first instance of his existence." [167] Moreover, society ought to protect human embryos because of their genetic uniqueness and potential to become persons. In this perspective, embryo research is a form of unjustified killing. Scientists cannot ethically learn whether embryo research can lead to significant scientific and clinical gains, since embryos would be destroyed in the process.

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[166] Appendix I to this paper presents a full spectrum of moral views on the moral standing of embryos and the degree of social protection embryos deserve in research activities.

[167] Vatican, Congregation for the Doctrine of the Faith. (1992). Instruction on respect for human life in its origin and on the dignity of procreation. In Alpern, D., ed. (1992). The Ethics of Reproductive Technology, (New York: Oxford University Press), 85; see also Doerflinger, R.M. (1999). Testimony before the Senate Appropriations Subcommittee on Labor, Health and Education, Jan. 26.

A second approach also appeals to the principle of respect for persons. However, this view holds that the biology of the human embryo counts against giving embryos any moral status that would prevent research to benefit patients, science, and society. For example, since twinning can occur in this period, "a determinate human being does not yet exist."[168] Further, without implantation and gestation to fetal viability and beyond, an embryo can have no interests that society ought to protect. In this view, embryo research poses no comparable moral claims of the type made by actual persons. This view of embryo research focuses largely on "brain life" as pivotal for authentic personhood.[169]

These conservative and liberal approaches collide sharply. Different worldviews and religious interpretations can lie in the background of these conflicts. In a commissioned essay for the NIH Human Embryo Research Panel, Steinbock discussed these views and their variants, noting origins in the abortion debate. [170] She

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[168] Lockwood, M. (1995). Human identiy and the primitive streak. Hastings Cent Rep 25, (Jan.- Feb.), 45.

[169] Lockwood, M. (1985). When does a life begin? In Moral Dilemmas in Modern Medicine, Lockwood, M., ed. (Oxford: Oxford University Press), 9-31.

[170] Steinbock, B. (1994). Ethical issues in Human Embryo Research. In National Institutes of Health, Papers Commissioned for the Human Embryo Research Panel, 30-32.

identified a third position as a "compromise between the conservative and liberal views," i.e., that "although embryos are not persons, they have moral value as a form of human life." In a section entitled "A Third Position: Embryos Have Symbolic Value," she discussed how several official panels that considered the ethics of embryo research adopted this position. [171]

The framework of "symbolic value" stems from Robertson's work on the ethics and law of embryo research. His framework for the status of the embryo is: "special respect but no rights for embryos." Respect is due, because the embryo is a "potent symbol of human life." [172] In Robertson's view, special respect takes the

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[171] See footnote 3. The Ethics Advisory Board (1979) found that "the human embryo is entitled to profound respect; but this respect does not ncssarily encompass the full legal and moral rights attributed to persons." (pp.35-6) The Warnock Committee's position was that "the embryo of the human species out to have a special status," and "should be afforded some protection in law." (pp. 63-4). The NIH Human Embryo Research Panel stated that "although the preimplantation human embryo warrants serious moral consideration as a developing form of human life, it does not have the same moral status as an infant or child." (p. x)

[172] "Special respect but no rights for embryos makes sense ifone views the underlying ethical and policy question as one of demonstrating respect for human life. If the embryo is too rudimentary in development to have interests, it may nevertheless be a potent symbol of human life." Robertson, J.A. (1995). Symbolic issues in embryo research. Hastings Cent Rep 37 (Jan-Feb), 37. Also, see his testimony before the NBAC. Jan. 19, 1999, pp. 81-87.

form of rigor of research review and fidelity to safeguards that ought to surround embryo research.

To date, NBAC's deliberations reflect a compromise view with significant differences from the Human Embryo Research Panel's perspective and recommendations. Commissioners appear to seek higher recognition of and empathy with important moral concerns within the opposing position than did the Panel's report, although the Panel's process could not be faulted along these lines.[173] Commissioner Charo is a critic of the "symbolic value" framework, because it is dismissive of the moral concerns and suffering of opponents of embryo research. She was also critical of the Human Embryo Panel's moral reasoning as too exclusively "bioethical" by focusing almost entirely on issues of moral status, rather than on political ethics and on justice issues in particular.[174] She has

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[173] "The Panel held six extensive meetings, heard 46 oral presentations, and received over 30,000 letters, cards, and signatures on petitions as a panel, plus uncounted hundreds of items of correspondence addressed individually to panel members. From the firt to the last day of the panel's work, there was constant and profound awareness of the high level of public concern about the sensitive and complex issues involved." Stephen Muller to Ruth Kirschstein, October 12, 1994. See footnote 7 above, at p. v.

[174] Charo, RA (1995). The hunting of the snark: the moral status of embryos, right-to-lifers, and third world women. Stanford Law & Policy Rev 6, 11-27.

made this same argument in other writings.[175] She was recused from NBAC's deliberations on PSC research. [176] However, her prior writings and talks on embryo and fetal research are very important to NBAC's considerations and clearly influence part of the argument in Part III. Although it requires some supplementary arguments, Charo's justice arguments are a promising direction for an ethics of compromise on FFER that is faithful to the legacy of the National Commission on FR. President Clinton's request to balance "*all* (emphasis added) ethical and medical considerations" can be seen as reinforcement for Charo's main point. Can there be *any* degree of overlapping consensus between the two views of the morality of embryo research described above?

C. Dworkin's Partly Unifying Principle

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[175] See footnote 20; also Charo, R.A. (1995). "La penible valse hesitation": fetal tissue research review and the use of bioethics commissions in France and the United States. In Bulger, RE, Bobby, EM, Fineberg, HF, eds, Society's Choices: Social and Ethical Decision Making in Biomedicine. (Washington, DC: National Academy Press), 477-500; Charo, R.A. (1996). Principles and pragmatism. Kennedy Institute of Ethics J 6, 319-22.

[176] Commissioners Charo and Greider were recused because they are employed by universities (Wisconsin and Johns Hopkins) with financial interests in PSC research (Thomson and Gearhart studies) and issues that NBAC will address in its recommendations. NBAC Proceedings, Feb. 2, 1999, p. 2.

Similar to the abortion debate, a single-minded focus on the moral status of the embryo has frozen debate on the ethics of embryo research into two polar opposites. Is there any hope for passage through these frozen straits? Ronald Dworkin made a significant effort [177] to locate common moral ground between liberal and conservative views on abortion.[178] Dworkin admits the stark polarization of the abortion debate and its baleful consequences for moral discourse. He is skeptical of the arguments given in several works[179] urging compromise that do not appreciate the moral depths of the divisions that exist or that argue for compromise while biased by one side of the debate.

> Self-respecting persons who give opposite answers to whether the fetus is a person can no more compromise, or agree to live together allowing others to make their own decisions, than people can compromise about slavery or apartheid or rape. For someone who believes that abortion violates a person's most basic interests and most precious rights, a call for tolerance or compromise is like a call for people to make up their own minds about rape, or like a plea for second-class citizenship,

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[177] Dworkin, R. (1993). Life's Dominion. An Argument about Abortion, Euthanasia, and Individual Freedom. (New York: Knopf).

[178] This section cites several key passages of this important work. Dworkin's insights are more appreciable in his own well chosen words.

[179] Tribe, L.H. (1990). Abortion, The Clash of Absolutes. (New York: W.W. Norton); Rosenblatt, R. (1992). Life Itself. (New York: Random House).

> rather than either full slavery or full equality, as a fair compromise of the racial issue.
>
> So long as the argument is put in those polarized terms, the two sides cannot reason together, because they have nothing to reason or be reasonable about. One side thinks that a human fetus is already a moral subject, an unborn chid, from the moment of conception. The other thinks that a just-conceived fetus is merely a collection of cells under the command not of a brain but of only a genetic code, no more a child, yet, than a just-fertilized egg is a chicken... [180]

However, Dworkin believes that conventional understanding of the polarized state of the debate is shrouded by intellectual confusion and can be clarified and dispelled. The confusion is due to a failure to distinguish between a "derivative" and a "detached" objection to abortion. The "derivative" type of objection -- to abortion as murder -- is derived from rights and interests that presumably all persons, including fetuses, can morally and legally claim. These rights begin with a right not to be killed. In this view, government has a "derivative" duty to protect fetuses from abortion.

A second type of objection to abortion, the "detached" type, objects to abortion as an assult on the sacred nature of human life in itself. Not dependent on particular rights or interests, it

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[180] See footnote 136 above, p. 10.

views abortion as wrong in principle due to its assault on the sanctity of human life at any stage. Dworkin concludes that:

> ..someone who accepts *this* objection, and argues that abortion should be prohibited or regulated by law for *this* reason, believes that government has a detached responsibility for protecting the intrinsic value of life. [181]

Having established this distinction, Dworkin goes to great lengths to argue that, despite the "scalding rhetoric" of the pro-life movement to the effect that the fetus is a moral person from the moment of conception, "very few people --even those who belong to the most vehemently anti-abortion groups -- actually believe that, whatever they say." [182] He also notes that few liberals view the fetus as simply mere tissue. He describes the views of most people about the issue of abortion and the duty of the government to protect the sacredness of life in the detached rather than derivative camp. If Dworkin is right, this distinction goes a long way to define the role of government in legislation about abortion and embryo research. The ban on FFER is clearly framed in a "derived" rather than a "detached" view of government's responsibility. A "derived" view will insist on virtually absolute protection of rights claimed for the fetus. A "detached" view will

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[181] See footnote 136, p. 11.

[182] See footnote 136 above, p. 13.

focus on the wrongmaking feature of abortion as a violation of the "intrinsic value, the sacred character, of any stage or form of human life."[183] Those who hold this view will believe that government ought either to prohibit abortion for this reason or, as government has done in Roe v. Wade and elsewhere in the states, to regulate it by law. The most liberal view of abortion would insist on minimal regulation of abortion and that law primarily protect intrusions on women's choices. Those who take the middle way will permit abortion but regulate it carefully by law. Prohibitions of abortion are appropriate when the fetus is viable, except in situations where abortion will avert threats to the woman's life or health. With exceptions in a few states, abortion law in this society has clearly been a "detached" rather than a "derivative" type that would prohibit abortion by law.

Dworkin's central hypothesis is that understanding what we as a people really disagree about in the abortion debate will unite rather than divide. He proposes:

> The disagreement that actually divides people is a markedly less polar disagreement about how best to respect a fundamental idea we almost all share in some form: that individual human life is sacred. Almost everyone who opposes abortion really objects to it, as they realize after reflection, on the detached rather than the derivative ground.

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[183] See footnote 136 above, p. 11.

> They believe that the fetus is a living, growing human creature and that it is intrinsically a bad thing, a kind of cosmic shame, when human life at any stage is deliberately extinguished.[184]

Dworkin proposes that the main difference between conservatives and liberals on abortion is not whether the fetus is or is not a moral person; it is in how these views interpret the claims that flow from the principle of respect for the sacredness of life. In a section on this proposition, he extends his central hypothesis:

> We should...consider this hypothesis: though almost everyone accepts the abstract principle that it is intrinsically bad when human life, once begun, is frustrated, people disagree about the best answer to the question of whether avoidable premature dealth is always or invariably the most serious possible frustration of life. Very conservative opinion, on this hypothesis, is grounded in the conviction that immediate death is inevitably a more serious frustration than any option that postpones death, even at the cost of greater frustration in other respects. Liberal opinion, on the same hypothesis, is grounded in the opposite conviction: that in some cases, at least, a choice for premature death minimizes the frustration of life and is therefore not a compromise of the principle that human life is sacred but, on the contrary, best respects that principle.[185]

Dworkin interprets disagreements between liberals and conservatives over abortion as arising mainly from varying interpretations of the scope and meaning of the principle of

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[184] Ibid.

[185] See footnote 136 above, p. 90.

respect for the sacredness of life. Conservatives view the "natural" contribution to life as preeminent, while liberals view the "human" contribution as supreme. To the former, the gift of life is more important than anything a person can do. The premature ending of life is the greatest frustration. To the latter, since human investment in life gives particular lives their creative value, significant frustration of that investment can call for decisions that life should end to prevent even more frustration.

In addition to his illuminating distinction between "derived" and "detached" objections to abortion, this passage is most relevant to the issue of FFER.

> We can best understand some of our serious disagreements about abortion [and embryo research]...as reflecting deep differences about the relative moral importance of the natural and human contributions to the inviolability of individual human lives. In fact, we can make a bolder version of that claim: we can best understand the full range of opinion about abortion, from the most conservative to the most liberal, by ranking each opinion about the relative gravity of the two forms of frustation along a range extending from one extreme opinion to the other -- from treating any frustration of the biological investment as worse than any possible frustration of human investment, through more moderate and complex balances, to the opinion that frustrating mere biological investment in human life barely matters and that frustrating a human investment is always worse.[186]

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[186] See footnote 136 above, p. 91

Respect for the Intrinsic Value of Life. Although language about the "sacredness" or "sanctity" of life is appropriate, one does not have to embrace the religious premises underlying these terms to agree with the direction of Dworkin's argument. Dworkin recognizes that some will not want to use it because of its religious connotations. He often uses "inviolability" of life or human life interchangeably with "sacredness." This principle can also be understood as respect for the intrinsic value of life. The term "intrinsic" points to the value of something in and of itself, independent of its results for or relations to ourselves or other persons. Dworkin gives examples of great art, cultures, animal species, and each individual human life itself, as meriting profound respect apart from their instrumental value to us or other persons. Although we are part of the whole that includes these creative events, processes, and beings, we can observe that they have their own moral status apart from any particular interests we have in enjoying or using them.[187] This independent standing is worthy of the awe with which believers perceive the inherently

[187] Without adopting the theological premises that gave rise to his work, one must note that Martin Buber's reflections on the distinction between "I-Thou" relations and "I-It" relations point to the same phenomena. (cite Buber)

"sacred" or "holy" quality of beings or of the profound respect with which others would view the same qualities.

How does Dworkin's work connect with the debate on FFER? First, it reduces the distance between the polarized sides and strengthens those who would take a middle way. Liberals and conservatives need not be permanently divided along lines of the the confrontation between the Human Embryo Panel report and the Congress' ban on FFER.

Using Dworkin's work, the debate about FFER becomes one about the meaning of respect for the intrinsic value of life. Conservatives and liberals are loyal to the same principle but interpret it in different ways. Conservatives desire not to interrupt an investment from either a biological or divine source (or both) in the embryo's unique life in spite of the frustration of human desires. Liberals value the good that can be done by relieving frustrated human investment in lives of sick and suffering children and adults.

The main effect of Dworkin's argument on the politics of FFER is to encourage a middle way for liberals and conservatives willing to embrace a "detached" role for government in issues on embryo research. Those on either extreme of the issue may reject the

argument, because they will not be persuaded to abandon "derivative" or rights-based positions. This means that liberals and conservatives nearest to the middle of the debate about FFER can join in protecting respect for the instrinsic value of human life by a decision to regulate embryo research in the United States in both the federal and private sectors.

Dworkin's principle so interpreted and specified can take us only so far into the heart of the argument. It helps mainly to frame the debate in terms of loyalty to a common principle and to a "detached" view of government's proper role. Despite its merits, the Dworkin principle will not yield a fulsome moral consensus for FFER, because it does not tell us why federal funding of embryo research can be ethically acceptable. Nor can the issue of moral status of embryos (or non-viable fetuses) be resolved at the level of ethical theory. Ethical theory can clarify and frame the debate about moral status, but it has not the authority finally to resolve such debates, because ultimate answers to such questions appeal to sources of inspiration beyond ethical theory that are metaethical or theological. Ethical theory does not supply the faith or belief in a guiding purpose in nature -- or the lack of faith or such belief, for that matter -- that shape beliefs about the moral

status of embryos or fetuses. In this realm of ultimate loyalties, the choices and commitments that persons make are hardly subject to convincing proofs.[188] In a democracy, the political process is a penultimate resource to resolve such issues.[189] Both Congress and the several states can choose to embody in law either a "detached" or a "derivative" view of the use of embryos in research and of government's role in protection and/or regulation. So does democracy function to ameliorate the divisiveness of otherwise irreconcilable moral positions.

A second argument, much more political in nature, is required to inspire resolve in conservatives to permit limited FFER, under strict conditions, and to restrain liberal resolve to secure FFER in Cases 2, 3, and 4 in order to maximize the scientific and clinical benefits of PSC research. Obligations of distributive

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[188] The issue of "wrongful life" in court cases and the issue of "personhood" in the context of embryo and fetal research can illustrate this point. There is a point in the arguments involved past which judicial authorities acknowledge that they cannot go with confidence that they are still in the realm of human and public affairs.

[189] In a democracy that prizes separation of church and state, there is no final arbiter of such issues as the moral status of embryos or fetuses, which raise questions about the ultimate meaning of life itself. This is properly viewed as a religious or philosophical pursuit, best addressed in the context of worship or other forums that have evolved to permit the free pursuit and expression of answers to the question.

justice explain why Congress can morally approve of FFER, provided that it legislates to regulate embryo research in loyalty to the principle of respect for the intrinsic value of life. Approval of FFER without regulation would forsake the Dworkin principle, because scientists then would be able to do anything they wished with embryos in research. This would be a flagrant violation of respect for the intrinsic value of life.

D. Putting Charo's Justice Principle to Work.

Commissioner Charo has written about the resources of political ethics and social justice for understanding and resolving disputes -- such as moral status -- that do not yield to ethical analysis of the type used in the Human Embryo Panel's report. She also counsels, out of a wealth of political experience, that approaches to resolving problems in justice require respect -- by those on both sides of issues -- of the loyalty to moral principles and values with which each holds their respective views. We can then speak of the Charo principle as one that combines justice-seeking political resolutions of deeply divisive issues with compromises by which conservatives and liberals convey respect for the moral integrity of their respective positions. The Dworkin principle is the best framework within which to appreciate how

conservatives and liberals could say with respect, "We begin from the same principle but interpret it in different ways." In my view, combining the Dworkin and Charo principles create the most promising moral framework to resolve the dispute about FFER in PSC research.

Charo's justice-based arguments are crucial to examining why FFER is morally acceptable. The Dworkin principle is essential to understanding why embryo research is open to moral challenge. Using a combined Dworkin-Charo approach, NBAC can reach moral consensus on particular cases, mid-level principles, safeguards, and FFER. The history of protectionist federal policy, international experience, and the best moral lights of the commissioners ought also to shape the consensus. NBAC can then make its recommendations regarding public policy and FFER as related to PSC research.

Charo's justice-based and political arguments are sufficient to complete the task of justification for FFER. However, these arguments are not sufficient to make the moral argument for long-range reform of federal policy on fetal and embryo research and regulation of infertility research. Claims of justice must be buttressed by obligations of beneficence and utility to guide this

task and to overcome the gap between practices in research at the beginning of human life in the private and public arenas.

Obligations of Distributive Justice in Appropriations for PSC Research. Beauchamp and Childress write:

> The term distributive justice refers to fair, equitable, and appropriate distribution in society determined by justified norms that structure the terms of social cooperation. Its scope includes policies that allot diverse benefits and burdens such as property, resources, taxation, privileges, and opportunities. Various public and private institutions are involved, including the government and the health care system.[190]

The claims of distributive justice bear directly on two political and ethical issues that will require compromises of liberals and conservatives. The first issue concerns legislation regarding appropriations for FFER to hasten the transition from Stage 2 to Stage 3 of PSC research, as described above in Part I, Section 2. The focus of Congress ought to be especially on appropriations to support the derivation of PSCs from embryos only to shorten the transition from Stage 2 to Stage 3, i.e., focused on the goal of clinical trials in humans of cell-replacement therapies for diseases that cause early death or severe debilitation.

A compromise between liberals and conservatives will be required to facilitate the appropriations process for FFER, but

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[190] See footnote above, p. 327.

only in a context of Case 2, if the arguments given in Part II are persuasive. Given the legacy of the National Commission and the history of federal policy and regulations on fetal and embryo research, one can assume 1) it is desirable to focus FFER on pre-clinical and therapeutic aims, rather than on Stage 1 concerns, and 2) that Congress should be aided in its assessments by the moral and public policy advice of an official ethics body.[191]

The basic argument is that FFER can be morally justified only under certain conditions and as a last resort to optimize a transition from Stage 2 to Stage 3 of PSC research. FFER should be limited to projects that clearly fit within the parameters of Stages 2 and 3. Given the history of federal policy (but not federal regulations), Congress should not be asked to fund derivation of PSCs from embryos during Stage 1, the scientific exploration of the properties of PSCs and cell lines derived from various sources. The present stage of political considerations, i.e., whether to permit the Rabb opinion to govern the NIH's funding of "downstream" PSC research, ought to be viewed as a moral

[191] My recommendation will be that, if NBAC is not still operational at this time, that this body be an EAB appointed by the Secretary, DHHS, for the specific purpose of advising the Secretary and Congress on the question of FFER in PSC research at that time. Existing federal regulations enable such a step to be taken. 45 CFR 46.204.

and political experiment in federal funding of PSC research.[192]

In consideration of federal funding of PSC research, it is reasonable to ask that if the transition period to clinical trials of cell-replacement therapies for diseases that cause early death and debilitation is five to ten years rather than three to five years, how many Americans of all ages will die whose lives could have been saved by a speedier transition? How much morbidity among the whole population could have be reduced by federal participation in the period of preparation for clinical trials to their conclusion? Would not FFER focused on Stage 2 research hasten the transition? These are legitimate questions of distributive justice that will be posed not only by ethicists, but by taxpayers who are voters in elections to come. Why should large numbers of Americans risk added earlier death and debilitation if Congress can act to prevent this possibility? These questions reflect a concern for justice in Congressional appropriations for the NIH and NSF but which could possibly benefit many citizens whose lives will

[192] NBAC and members of the Administration and Congress can help to create a vision of the moral and political implications of where permitting (with eyes wide open to the derivation of PSCs from embryos using private funds) NIH "downstream" funding can lead, i.e., to creative and moderate reforms of the polarized and incoherent extremes of American research practices in the private and public arenas.

otherwise be shortened and health destroyed. A positive result from the clinical trials will obviously be beneficial in terms of reduction of mortality and morbidity; a negative result will also have preventive benefits, i.e., it will refute arguments for any further trials with the same premises and design and protect human subjects from risks of trials with erroneous scientific aims.

Congress is obligated to appropriate funds for research fairly. When it comes to the aim of funding in Stage 2 of PSC research, it would be fair to support scientists obligation to learn whether PSCs derived from ES cells will be as good or better progenitors for therapeutic cell lines as PSCs derived from EG cells, but only if it is morally acceptable to pursue such knowledge. Federal funding of derivation of PSCs from embryos is now illegal, while funding derivation from fetuses is legal. The compromise would ask Congress for the first time to fund the former, but only under a set of strict conditions.

The compromise limits FFER to Case 2 and then only to the pre-clinical period prior to clinical trials and to actual clinical trials in humans, rather than for the entire period of scientific preparation for clinical trials. Pre-clinical activities would include testing efficacy in animal models for human diseases, in

vitro experiments to gather pre-clinical information, and in vivo testing of components of the proposed process of cell-replacement therapy.

This compromise will seem unfair to the liberal mind's overally assessment of justice issues and FFER. However, the chances of reaching a satisfying moral compromise to permit political action will be higher if FFER is focused exclusively on on a) therapeutic intent, albeit for living human beings rather than for embryos, than on b) uses to obtain biomedical knowledge otherwise not obtainable; i.e., knowledge of the properties of PSCs and cell lines derived from embryos, fetuses, adult stem cells, and possibly SCNT-generated embryos.[193] Given the history of federal

[193] Note that the compromise fits with the two categories of research protected by federal regulations on fetal research (described in Part I, Section 3) and extended to FFER. The compromise also assumes a "detached" view of the government's role in protecting embryos in research, i.e., expressed by a carefully regulated practice with safeguards to prohibit or minimize abuses. Most importantly, any compromise that permits FFER (for the first time, even in the context of therapeutic intent) must assume the construction of federal regulations of embryo research that unify practices in both the public and private sectors. In this respect FFER, limited to Case 2, could be the opening chapter in a future history of moderating all of the overly protectionist public policies on FR and FFER that are the legacies of the political cultures of the 1980s and 1990s. What better way (in research activities) to show respect for the instrinsic value of life than to reform by the politics of compromise the overly permissive morality of the private sector and the overly protective morality of the public sector into a new and unified public policy for

policy on embryo research and the potential for divisiveness of the issue, it is better to leave all funding for derivation of PSCS from any source for Stage 1 to the private sector, with the exception of Case 3. Among NBAC's recommendations can be one to the effect that the private sector is obligated not to proceed with Case 3 research without public discussion, in a forum such as NBAC or the NIH-RAC, of the ethical rationale and goals for such activities. The private sector assumed this obligation during the early years of DNA research without any objection.[194]

In regard to public policy recommendations for federal funding of PSC research, NBAC may consider adopting some or all of the conditions presented in Table 3.[195]

Table 3. Conditions Sufficient to Warrant FFER To Transition to Clinical Trials

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embryo and fetal research? Such an effort to reform research ethics at the beginning of human life could also be the beginning of efforts to expand the circle of morally and constitutionally protected considerations to all living human subjects of research, regardless of the source of financial support of research.

[194] Cite Cook-Deegan on this point?

[195] These conditions were expressed, in principle, in remarks made by Commissioner Childress, in the NBAC meeting in Charlottesville, VA, on April 16, 1999.

- NIH-NSF "downstream" funding of PSC research combined with support from the private sector has effectively led to understanding of cell differentiation, differences between EG and ES cells, and other scientific goals of Stage 1 of PSC research.

- Scientists have learned, through research with animal and human PSCs and cell lines, how to avoid the tumorigenic dangers and other known risks of using ES cells.

- The NIH-NSF scientific peer review process is in agreement that strong scientific support exists to enter a pre-clinical period prior to clinical trials of cell-replacement therapies in humans for one or more diseases that are life-threatening or severely debilitating; e.g., Type I diabetes, leukemia, Parkinsonism, etc.

- A qualified panel of scientific experts makes the case that FFER is required, in the context of Case 2, as a last resort to complete the pre-clinical period and condict clinical trials in humans; i.e., there are no other satisfactory alternatives to using live embryos for the purpose of deriving PSCs to develop cell lines for therapeutic purposes.

- Congress had previously received recommendations from NBAC to the effect that considerations of social justice and other ethical principles justified FFER in the case of "excess" embryos donated by parents in treatment for infertility. Before taking the step of approving FFER in the context of Stage 1 and 2 activities, Congress would receive the moral and public policy advice of NBAC. If NBAC is not operational at this time, an EAB appointed by the Secretary, DHHS for this purpose, may so advise the Congress.

- Appropriations for PSC research in Stage 2 may only be used in to fund research in centers that assure the NIH or NSF that a) IRB approval has been obtained for a two-stage consent process that separates IVF decisions from decisions to donate embryos for research and a plan to

protect the privacy of donors, and b) that such research to be done with donated embryos conforms to the guidelines recommended by the NIH Human Embryo Research Panel. No awards or contracts can be processed without satisfying these stipulations.

¯ Appropriations for PSC research in Stage 3 include the conditions for Stage 2 funding, including additional Congressional action to assure fairness in selection of subjects as donors of embryos and as participants in the initial and succeeding clinical trials of cell-replacement therapy.

These conditions would be probably be sufficient to move moderate conservatives with a "detached" view of government protection of embryos to agree to FFER in Case 2. It is true that liberal members could probably approve FFER in Case 2 today. However, support for an approach of "last resort and no satisfactory alternative" conveys respect for sincerely held moral views of conservatives, as would limiting FFER to a context of therapeutic intent. This compromise by liberals fits well with the obligations of the Charo principle.

Specifications of Justice in Research Activities. If Congress were able to compromise and approve FFER under these conditions, moral concern would also exist about obligations of justice in two contexts of selection of subjects: 1) selection of donors of embryos as sources of PSCs, and 2) selection of participants in clinical trials of cell-replacement therapy. The Belmont Report

states that the claims of justice in research activities requires the fair distribution of benefits and burdens of such activities over a whole population.[196] Federal non-involvement in infertility research and the ban on FFER have already combined to infringe on obligations created by this principle in one actual and one future way: 1) the composition of the pool of donors of embryos in Case 2 is limited to private patients in infertility centers, and 2) if not prevented by a deliberate plan, the selection of subjects to participate in clinical trials of cell-replacement therapies could be biased by inequities that inhibit access to clinical trials, especially for poor and disadvantaged Americans. Steps to prevent biased selection of subjects in each of these contexts could be mandated by Congress as part of its appropriations process.

Consider the moral implications of the fact that the pool of donors of embryos in Case 2 is entirely composed of private patients in infertility treatment. Women or couples who donate

[196] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979) The Belmont Report. FR Doc. 79-12065, p. 5. This classic statement of the principles that govern biomedical research with human subjects discusses justice primarily in terms of the fair distribution of risks and vulnerabilty of certain groups for recruitment. It does stress that "whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands that these not provide advantages only to those who can affford them.."

embryos are not "human subjects" in a primary sense of being acted upon by researchers. The woman is acted upon by a specialist in reproductive medicine. Later, researchers may use her embryos in research activities. Such women and couples are, however, human subjects in a secondary sense. They have interests of voluntariness, comprehension, privacy, and justice that are protected by the ethics and regulations of research with human subjects. It follows that all Case 2 research ought to be submitted to IRBs for prior review. IRBs ought to be concerned with plans for a two-stage informed consent process as described in Part II in discussion of Case 2. Further, researchers should not be able to link embryos they receive by donation with identifiable donors. No identifiers should accompany the transmittal of embryos from the setting of therapy to the setting of research, in the interest of protecting donor privacy. Finally, both IRBs and Congress ought to be concerned about the disproportionate and unjust distribution of benefits and burdens that would be involved in accepting without question the present population of donors in Case 2 as sources of donation.

Consider the situation of economically disadvantaged persons who are infertile and of infertility patients in the private

sector. These persons are also taxpayers. The costs of infertility treatment are prohibitively high. One of the chief causes is lack of federal scientific involvement and regulation. Economically disadvantaged persons in the United States receive very little treatment for infertility, in spite of a higher rate of infertility among African Americans.[197] Although a small number of states have required some degree of health insurance coverage of infertility treatment,[198] no state Medicaid program reimburses for it. [199] Ideally, low-income infertile couples ought to be receiving treatment and positioned to share the benefits and burdens of experimental treatment and embryo donation. Yet, the combined effects of the history of federal abandonment of infertility research and the ban on FFER work to impose all of the risks of embryo research upon private infertility patients. If they decide to donate, they will have borne the risks of IVF or other procedures required to produce embryos at all. These patients do

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[197] "The incidence of infertility is 10.5 among married couples with non-Hispanic black women, roughly 1.5 times greater than among Hispanic or non-Hispanic white women." Cited in New York Task Force, see footnote above, p. 11.

[198] New York State Task Force, see footnote above, p.432.

[199] Personal communication, American College of Obstetrics and Gynecology, April 15, 1999.

receive the benefits of slowly improving techniques of infertility treatment. However, the risks they accept are of special concern due to lack of public oversight and regulation of embryo research. These are gross contradictions and inequalities in social practices of research. Present public policies are unfair to all taxpayers with a condition of infertility.

To prevent bias in the selection of subjects for embryo donation, Congress will need to take steps well in advance of Stages 2 and 3 of PSC research to encourage states through the Medicaid program to fund infertility treatment for infertile couples eligible for Medicaid. Funding of the federal share of the Medicaid program for this particular purpose would go a long way towards assuring the states' funding of their share. Such action by Congress would be an appropriate remedy for past neglect of the unfairness with which infertility treatment is distributed, as well as an appropriate step to assure that the obligations of justice would be followed in selection of donors of embryos for federally funded PSC research.

The issue of equity in selection of subjects is addressed --in part -- in federal regulations governing criteria for IRB approval

of research.[200] Since the regulations do not address directly the issue of equity of access to the potential benefits of clinical trials, Congress will need to accompany its appropriations for PSC research with stipulations that recipients of such fundings must assure their local IRBs that reasonable steps have been taken to make access to clinical trials of cell-replacement therapy available to "economically...disadvantaged persons." Additional funding for education of the public at large, including minorities traditionally wary of participating in research, ought to be appropriated to insure that recruitment of subjects occurs after appropriate public education has had a chance to succeed. By this step, Congress can avoid criticism that it did not take every reasonable step to assure that the public understands the rationale

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[200] IRBs are required, among other things, to determine if "selection of subjects" for the proposed project "is equitable." 45 CFR 46.111 (3). The IRB is to take into account the purposes of the research, the setting in which it is to be conducted, and be especially "cognizant of the special problems of research involving vulnerable populations, such as children prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons." The history of these provisions are marked by protection such vulnerable persons from exploitation in research or biases in selection that would expose them to higher risks. IRBs should be equally concerned with the issue of fairness in selection of subjects to improve access to the potential benefits of clinical trials, especially for "economically..disadvantaged persons," since participation in clinical trials is heavily biased already in favor of more advantaged groups.

for FFER and that federal policy is to overcome past inequities of access to the potential benefits of clinical trials. A majority of conservatives and liberals should be able to agree readily to such a provision. This concludes the section on the moral and political argument to support FFER in PSC research.

E. Long Range Reforms: Obligations of Beneficence and Utility

The discussion has referred several times to a need for long-range reforms. Federal policy on FR and ER is too protectionist to serve the public interest fairly in a scientific context of the completion of the Human Genome Project (HGP) and prospects for success in stem cell biology. The section concludes with a discussion of the need for long-range moderation and reform of federal policy on research at the beginning of human life.

For those who hold moderate or a "detached" view of government's role in protecting fetuses and embryos in research, strongly protectionist policies seriously infringe on moral obligations of beneficence and utility. Considerations of the claims of these principles need to be added to the considerations of distributive justice reviewed in the previous section. When the ban on FFER is combined with federal inaction on regulating infertility research and a virtual ban on federal funding of FR,

the cumulative effects on the losses of basic knowledge and pre-clinical opportunities amount to grievous violations of obligations of beneficience and utility. [201]

Obligations of Beneficence and Utility. The "principle of beneficence refers to a moral obligation to act for the benefit of others."[202] Obligations flowing from beneficence shape medicine's goals of healing and promoting health,[203] tempered and balanced by commitments to avoid or minimize deliberate harm [204] and to

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[201] There were no hearings or Congressional testimony regarding the scientific or clinical consequences of the ban on embryo research prior to its passage.

[202] Beauchamp, T.L., Childress, J.F. (1994). The Principles of Biomedical Ethics. (New York: Oxford University Press), p. 260.

[203] 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 activities that serve the goals of medicine (e.g., prevention and research) under healing. Actual experience recommends viewing medicine as having multiple, complex, and sometimes competing goals: e.g., healing, promoting health, and helping patients achieve a peaceful and dignified death. 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.

[204] A traditional ethical norm of medicine is "Above all (or first) do no harm" which is transmitted in the ethical principle of non-maleficence. See Beauchamp, T.L., Childress, J.F. (1995). Principles of Biomedical Ethics. 4th edn. (New York, Oxford University Press), p. 189.

considerations of utility. The principle of utility [205] "is limited to balancing benefits, risks, and costs (outcomes of actions), and does not determine the overall balancing of obligations."[206] Utility is a less weighty moral principle than beneficence, but loyalty to it creates obligations that shape the role of science in a modern democratic state. Loyalties flowing both these same principles (beneficence, non-maleficence, and utility) also shape the moral traditions of biomedical research. These research activities are not morally independent but are encompassed by the morality of medicine, which is accountable to structural values of democratic societies, including respect for persons, social justice and liberty.[207]

In the relations between modern medicine and biomedical research, considerations of utility have strongly influenced the standard of care.[208] There is an obligation to <u>prove</u> whether

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[205] This principle is also called proportionality.

[206] Ibid., and p. 261.

[207] It is this understanding of the role of medicine and biomedical research within the structural values of society, i.e., as accountable to moral principles expressing those values, that empowers public bioethics to address moral problems without qualification as to whether these occur in the public or private spheres.

[208] Define standard of care.

existing treatments and procedures are safe and effective. The criterion of proof is the experimental method. The same standard holds with new or innovative treatments or procedures; i.e., the obligation is to compare the safety and efficacy of the new with existing treatments or procedures which may be proven or unproven. The obligation to learn experimentally how best to treat and prevent disease is a requirement of utility aimed to maximize obligations of beneficence.[209]

When it comes to promising prospective treatments or procedures, such as cell-replacement therapies developed from PSCs, loyalty to utility obliges investigators first to learn whether a clinical trial in humans is well-founded scientifically and pre-clinically. Stages 1 and 2 of PSC research, as described above, are aimed to carry out this obligation. This obligation is a necessary but not sufficient basis upon which to conduct a clinical trial in humans. Prior to consideration of the ethical question, "Ought this trial in humans be done at all?", the investigators

[209] Alta Charo discussed a "civic duty" to volunteer for research, which must be balanced with principles of good government and distributive justice. [Belmont Revisited Conference, April 17, 1999] In biomedical research, there is a corresponding "scientific duty" to learn how best to treat disease by the scientific method, that must also be balanced by principles of non-maleficence and distributive justice.

must have satisified a scientific and a pre-clinical question: "Is there sufficient scientific understanding of the disease process and the action of the proposed treatment?" "Have results been achieved and replicated in suitable animal models that lead rationally to a prospect of benefits in humans?" With one exception, physician-investigators who bypass the scientific and pre-clinical stages of learning betray the canons of good science and loyalty to utility.

Exceptions to Obligations of Utility. The exception is when it would be clearly unethical to obtain the information to learn how to answer the scientific question. In such a case there could be an overriding reason to bypass the scientific stage of investigation. A good historical example is in the debate about the moral acceptability of uses of data obtained by German scientists who conducted experiments on political and concentration camp prisoners under the Nazi dictatorship.[210] Is it ethical to cite or use such data in the process of science today? In practice most scientists avoid using or citing this body of data out of respect for the victims of the moral horrors of the Holocaust.

[210] Citations needed.

Another example for discussion of exceptions to the obligations of utility occurred during planning for Protocol 076, which tested the drug AZT in HIV-infected pregnant women to prevent transmission of the HIV virus from infected pregnant women to their fetuses.[211] Was there an obligation to learn, by doing FR in the context of elective abortion, how and when the HIV virus is transmitted in utero before giving a drug with then unknown fetal side effects and the potential to cause birth defects in the fetus?

[211] At the time the 076 Protocol was first discussed at the NIH in 1986, the author was Chief of the Bioethics Program at the Magnuson Clinical Center. He raised questions about the scientific and moral adequacy of a trial of a toxic drug in utero in advance of gaining understanding of how and when the HIV virus was actually transmitted in utero. The only evidence available about HIV transmission was from the tissues of abortuses which suggested that transmission was later rather than earlier. However, this evidence was only partial and did not prove how and when transmission occurred. A way to answer this question definitively would have been to conduct a serial study of fetal blood drawn before and after elective abortions in the first and second trimesters of pregnancy. During the next year, the author joined the faculty at the University of Virginia but remained in dialogue with NIH scientists about the 076 Protocol and the issue of scientific and pre-clinical obligations. The regulations on FR and the "Golden Rule" law as passed by Congress clearly would prohibit such a study without a "waiver" from the Secretary, DHHS. There being no EAB, the author was advised by former member of Congress, Paul Rogers, to approach Congress with a request to the Secretary to waive the minimal risk requirment. The author sought support for this idea from several officials at the NIH, who were reluctant to support or accompany him on this mission. In point of fact, the O76 Protocol was successful in reducing transmission, and the investigators were lucky in their guess that HIV was transmitted later rather than earlier in pregnancy.

Protocol 076 was fortunately successful,[212] but it was not (in my view) based on the soundest of scientific foundations, because when the trial began, how and when HIV transmission in utero truly occurred was unknown. Ethical considerations and public policy, at the time, prevented these foundations from being laid. In retrospect, it is worth raising the question again as to whether FR in the context of abortion would have been morally justified to answer the question of how and when HIV is transmitted in utero. Virtually everyone would agree that it would be unethical deliberately to expose fetuses in the context of abortion at various stages of pregnancy to the virus in order to learn if it could be transmitted. However, would not the 076 Protocol have been a scientifically and ethically sounder study if this knowledge had been obtained by research in the context of abortion?

Long-range reforms of virtual bans on federal funding of FR are needed if the obligations of beneficence and utility are to be followed by scientists in the federal sector. Such bans defeat an obligation to build a knowledge base for experimental treatment. A good illustration is the effects of federal policy on FR required

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[212] Connor, E.M., Sperling, R.S., Gelber, R., et. al. (1994). Reduction of maternal-infant transmission of human immunodeficiency virus type I with zidovudine treatment. N Engl J Med 331, 1173-80.

prior to in utero gene transfer experiments.[213] The result is a dearth of information about normal fetal physiology and development required for sound fetal therapy experiments. For example, ignorance about fetal immunocompetence was a prominent topic [214] 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[215] 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. Federal policy on fetal research creates an

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[213] The language of the embryo ban reflects prior federal policy on fetal research extended onto embryo research.

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

[215] National Institutes of Health. Prenatal Gene Transfer: Scientific, Medical, and Ethical Issues. Third Gene Therapy Conference, January 7-8, 1999.

acute knowledge deficit even while the technical feasibility of ultrasound-guided fetal gene therapy steadily grows.[216]

Consider the consequences of protectionist federal policies for parents at *known* higher risk of transmitting genetic disorders to their children. How many persons fit this situation? Although the total number is hard to ascertain, one can posit numbers in relation to other established facts. These are the parents of between one-fourth and one-third of all children admitted to pediatric units in Western nations.[217] These children need treatment for the complications of genetic diseases, congenital malformations, or mental retardation. These are the parents of the approximately 22 percent of newborn deaths in developed nations caused by congenital malformations or genetic disorders.[218] These are the parents who choose prenatal diagnosis to ascertain whether their fetus and wanted child-to-be has inherited a genetic or

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

[217] Brent, R.L. (1985). The magnitude of congenital malformations. In: Preventiaon of physical and mental congenital defects. Part A. The scope of the problem. (New York: Alan R. Liss), 55.

[218] Galjaard, H. (1984). Early diagnosis and prevention of genetic disease. In: Galjaard, H., ed. Aspects of genetic disease. (Basel, Switzerland: Karger), 1.

chromosomal anomaly. All of these parents are also federal taxpayers.

The moral situation of parents at higher genetic risk is fraught with controversy made worse by an incongruent federal policy. On the one hand, these parents are confronted with successes of the HGP. On the other hand, they are confronted by a federal policy forbidding funds for promising research to open avenues to treatment. With the help of their taxes, diagnosis of hundreds of genetic diseases is now possible, including in the fetus. This list will grow to thousands and include genes that create susceptibility to common disorders like cancer, heart disease, and diabetes.

Consider the advances of the HGP in genetic diagnosis compared with the paucity of treatments for genetic disease. Genetic testing raises raise morally troubling questions for those with a strong family history of cancer, in part due to the perceived risks of genetic discrimination in health and life insurance. [219] However, the risk of discrimination pales in the face of the stark fact that there are few effective treatments for the genetic

[219] Collins, F.S. 1996. BRCA1 -- lots of mutations, lots of dilemmas. N Engl J Med 334, 186-88; Parens, E. 1996. Glad and terrified: on the ethics of BRCA1 and 2 testing. Cancer Invest 14, 405-11.

conditions that can be diagnosed. The wide gap between genetic diagnosis and treatment is the single greatest scientific and moral problem [220] facing the nation that largely created and funded the HGP. Closing this gap ought to be a major goal of federal science and health policy. PSC research is profoundly important in closing this gap. Protectionist policies maintain the gap and directly collide with the goals of medicine to heal and promote health. If the gap were closed, the opportunities of therapy for genetic disorders would create great pressures towards universalizing these benefits. Progress in genetic therapies could be a powerful force, working together with other pressures, towards more universal health care reform.[221]

A final reason to prefer long-range reform to continuing the ban FFER is to postponement of the task of adopting a more moderate and fitting public policy to regulate this entire area. Privately

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[220] The gap is a moral problem because treatment for genetic disease is more fitting with the goals of medicine than selective abortion to prevent or avoid it. If the gap ought morally to be closed, and it can be closed more quickly with Congressional action, then it follows that there is a significant moral problem affecting the Congress and the whole nation.

[221] Fletcher, J.C. (1998). The long view: how genetic discoveries will aid healthcare reform. J Women's Health, 7, 817-23.

funded embryo research is conducted widely on the fringes of public life. At best, traditions of self-regulation in science and medicine guide these activities. The worst case moral scenario is embryo research done without accountability to any source of authority, public or private. As NBAC and the Congress consider the specific tasks ahead in making federal funding of PSC research possible, it is worth remembering the additional benefits that could flow from research activities 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.[222]

Conclusions and Recommendations to NBAC.

This paper has discussed three moral problems or concerns in PSC research: the moral legitimacy of access to sources of PSCs, considerations of uses of PSCs in research, and the cumulative moral effects of the ban on FFER and other protectionist federal policies. The history of FFER in a larger context of other controversies and restrictions on federal funding of research at the beginning of human life found a significant difference between a moderate legacy of the National Commission (and subsequent federal regulations on FR) and the strongly protectionist policies that have been imposed by Congress. In part, the paper argues for a return to this legacy and its confidence in the potential for conflict resolution of an EAB to serve the branches of government in on issues of research ethics.

The paper discussed the tasks of NBAC in reviewing PSC research, as well as the strengths and weaknesses of an incremental or case-by-case approach to four sources of PSCs. It concluded

[222] As recommended for federal funding by the NIH Human Embryo Panel, see footnote 7 above, at p.

that moral justification for federal funding of PSC research is far easier to make in Cases 1 and 2 than in Cases 3 and 4.

The final part of the paper assumed that new principles were necessary to meet the challenges of justifying FFER in the context of PSC research. A discussion followed of the relevance of the (so-called) Dworkin and Charo principles to this task. Commissioners and other readers, including members of Congress, can decide whether or not these arguments are persuasive. If they are, Congress should not appropriate funds for FFER in PSC research without stipulating the conditions that appear in Table 3 and without additional legislation to assure that obligations of justice and the protection of human subjects of research are met.

Finally, the paper invites NBAC to consider its tasks with regard to PSC research aware that these tasks converge with needs for long-range reforms of a) overly protectionist policies on federal funding of research at the beginning of human life, b) overcoming the incongruities and contradictions that result from permitting radically different moral approaches to govern such research activities in the private and public sectors, and c) extending the moral and constitutional protection of human subjects

of research to all Americans regardless of the sources of funding for research.[223]

[223] The author is grateful to NBAC for the opportunity to assist it wth the task of responding to the President's request to consider issues of such complexity and import for the nation's health and for prospective treatment of diseases which cause early death and severe disability.