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VOLUME IX SUPPLEMENT: STEM CELL SYMPOSIUM

The Once and Future Debate on Human Embryonic Stem Cell Research

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In one Petri dish are scores, perhaps hundreds, of thrombocytes: human platelets, the cells that circulate in our bloodstream and help us stop bleeding when we're cut. Normally, platelets are produced when they bud off from megakaryocytes, their parent cells, in our bone marrow. The newly formed platelets circulate around our bodies for about a week, and then—if they haven't been used in clotting—they are destroyed in the spleen and liver, to be replaced by freshly created cells. But the platelets in this Petri dish have never been inside a bone or traveled through a vein or an artery; they will never encounter a spleen or a liver; they will never be a part of a human body or pumped by a heart. Only a few weeks ago, these cells were undifferentiated human embryonic stem cells,

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floating in this same Petri dish like clouds in a tiny sea of gel. Now, having been bathed by a researcher in the right combination of materials, they have become platelets.

In a neighboring Petri dish there are still clouds floating: human embryonic stem cells from the same line as those that have already been transformed into platelets. These cells are being cultivated, divided, and multiplied. They will supply the researcher with an essentially limitless number of genetically identical cells on which to test and re-test techniques for inducing thrombocytic differentiation—for making specialized human blood cells without blood, bone marrow, or a human body.

In these two Petri dishes we see the twofold magic of stem cells: they have the ability to replicate themselves repeatedly, and they can transform into a diverse range of specialized cells. So-called "embryonic" stem cells are taken from what is in fact the pre-embryonic blastocyst stage of development (i.e., a fertilized egg that has divided into a small cluster of cells).[1] They have the capacity to develop into every kind of cell. So-called "adult" stem cells are found at numerous sites around the body at every post-embryonic stage of development. They have the capacity to differentiate into a range of specialized cell types found in their organs of origin; this permits them selectively to repair and replenish specialized tissue.

Both adult and embryonic stem cells have tremendous potential for exploitation in the development of therapies for disease. The fact that they can self-replicate indefinitely means that they are of great utility in testing and comparing cellular responses to different drugs and biological materials. Moreover, if scientists can master the mechanisms by which stem cells can be made to differentiate into specialized cell types, stem cells may become a source of replacement cells for people with cellular diseases like diabetes, Parkinson's and Alzheimer's.

There is considerable doubt, though, about scientists' ability to attain that mastery. Some kinds of adult stem cells have already been used successfully in therapies (most familiarly in bone-marrow transplants for leukemia).[2] For the adult stem cell types with the most limited potential for differentiation, however, it can be challenging to harvest and grow sufficient numbers of cells to conduct research into the mechanisms by which they differentiate. Embryonic stem cells can be propagated easily, but researchers are only at the very beginning stages of understanding their differentiation and the mechanisms by which that differentiation is maintained. Differentiated stem cells have a disturbing tendency that scientists do not well understand to revert to an undifferentiated state,

1. *See, e.g.*, National Institutes of Health, Stem Cell Basics, Chapter III: What are embryonic stem cells?, http://stemcells.nih.gov/info/basics/basics3.asp (last visited Apr. 21, 2009).

2. *See, e.g.*, National Institutes of Health, Stem Cell Basics, Chapter IV: What are adult stem cells?, http://stemcells.nih.gov/info/basics/basics4.asp (last visited Apr. 21, 2009).

higgledy-piggledy, thus generating tumors.

In addition, the problem of rejection remains. Even if scientists could reliably cause embryonic stem cells to differentiate into exactly the sort of specialized cell required for a therapy, it is likely that just as with donated organs, the differentiated cells will be rejected by the immune system of nearly anyone into whom they were introduced.

One possible solution to this rejection problem involves therapeutic cloning. To illustrate this solution, suppose you need replacement cells of a certain sort. A scientist could remove the nuclear genetic material from one of your readily sampled cells—a skin cell, say. She could then enucleate (pop the nucleus out of) a donated human egg and pop your own nuclear material in. This would result in a clone of your cell: the equivalent of a fertilized egg with your exact genetic material in its nucleus (though it would have different mitochondrial DNA—the DNA in what we might think of as the "white" part of the egg surrounding the nuclear "yolk").[3] Scotland's famous Dolly the sheep was cloned in just this fashion. But the aim of therapeutic cloning is not to implant the egg into a woman's uterus and bring your cloned offspring to term. (That would be "reproductive cloning.") Instead, scientists permit the fertilized ovum to develop in a Petri dish for only a few days, until it reaches the blastocyst stage, and then harvest the embryonic stem cells. These cells are then influenced to differentiate *in vitro*—the Latin phrase means "in glass" and indicates that the process is occurring in a Petri dish rather than in the body—into the sort of specialized cell that you need. (This is called "therapeutic" cloning because it is undertaken for the sake of generating a therapy.) If all has gone well, your body will not reject the new replacement cells, because they contain your very own nuclear DNA (and thus produce identifying "tags" identical to the other cells in your body). While this procedure is still highly theoretical in terms of its therapeutic benefits, in 2008, some American scientists reported the successful cloning and development of a human embryo to the blastocyst stage using a donated egg and nuclear material taken from the researchers' skin cells.[4]

Over the past several years, the type of research described above has been the subject of a vigorous national debate. Adult stem cell research (and, for the most part, embryonic stem cell research conducted in laboratory animals) has been fairly uncontroversial. But human embryonic stem cell research involves

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3. *See, e.g.*, Genetics Home Reference, Mitochondrial DNA, http://ghr.nlm.nih.gov/chromosome=MT (last visited Apr. 21, 2009) ("Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. This genetic material is known as mitochondrial DNA . . . .").

4. Andrew Pollack, *Cloning Said To Yield Human Embryos*, N.Y. TIMES, Jan. 18, 2008, at A15.

the destruction of human embryos, and research using therapeutic cloning not only creates embryos that will eventually be destroyed in research, but also brings us uncomfortably close to human *reproductive* cloning—though there have not been known attempts to bring an actual human clone to term. The national debate has been concerned predominantly with the question of whether it is morally permissible to conduct human embryonic stem cell research at all. In general, that debate pits concerns about the moral status of the human embryo *in vitro* against the potential of embryonic stem cell and cloning research to deliver lifesaving and life-enhancing cures.[5]

One argument in this debate holds that the research is morally impermissible no matter what its potential therapeutic upside might be. This argument assimilates the destruction of the embryo to murder. For example, when White House spokesman Tony Snow was asked why President Bush vetoed federal funding for embryonic stem cell research, he replied, "The simple answer is he thinks murder is wrong."[6] According to a frequently used version of this argument, once fertilization has occurred, the resulting embryo is a human being like any other, and it deserves our full moral regard and protection.[7] Following this argument, no amount of benefit from research can justify what is seen as the conduct of mass murder in stem cell labs. Of course, many who advance this claim also attempt to undercut others' positions by arguing that the medical potential of stem cell research has been exaggerated—but the core of the argument is that the embryo *in vitro* has full moral status as a human being.

On the opposite side of the debate, another argument holds that genetic material notwithstanding, the early embryo either is not yet a human being, or is not yet (in developmental terms) the kind of human being who deserves our full moral regard.[8] According to this view, an early human embryo is merely a collection of cells with no strong moral claims upon us. For this position, too, the

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5. A secondary debate, relating only to therapeutic cloning, concerns the fact that cloning research relies upon women to volunteer to donate eggs via an invasive surgical procedure. For example, Dr. Leon Kass, Chairman of President Bush's Council on Bioethics, has questioned the morality of therapeutic cloning in part because it "exploits women as egg donors not for their benefit." Gina Kolata, *Koreans Report Ease in Cloning for Stem Cells*, N.Y. TIMES, May 20, 2005, at A1.

6. *Bush Spokesman Retracts Stem Cell Comment*, N.Y. TIMES, July 25, 2006, at A16. Press Secretary Snow later retracted this comment, clarifying that President Bush believes that human embryonic stem cell research involves "the destruction of human life." *Id.*

7. *See, e.g.*, PRESIDENT'S COUNCIL ON BIOETHICS, MONITORING STEM CELL RESEARCH 76 (2004), *available at* http://www.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf ("This view holds that only the very beginning of a new (embryonic) life can serve as a reasonable boundary line in according moral worth to a human organism, because it is the moment marked out by nature for the first visible appearance in the world of a new individual.").

8. For a summary of versions of this argument, see *id.* at 78-84.

actual efficacy of the cloning and embryonic stem cell research programs is not terribly important, since hardly any justification is required for what is seen as the mere destruction of some cells. Supporters of this argument attempt to bolster their pro-research position by touting the medical potential of embryonic stem cell research; however, the core of the argument is that the tiny group of cells in the dish has no moral status.

Between these opposites is a third position that casts the issue as involving the balancing of serious and competing moral claims. According to this argument, human embryos *in vitro* enjoy substantial moral status. Their destruction in research may nonetheless be permissible, however, if either or both of the following conditions are fulfilled: 1) the embryos' moral claims are outweighed by the potential of the research to alleviate human suffering; or 2) the embryos, if not used in research, would languish in the freezers of fertility clinics and eventually be destroyed.

Though this debate continues to rage in journals and on the Internet, as a policy matter it has been resolved in favor of permitting research on embryos, including embryos specifically cloned for research. Pursuant to a statement made by President Bush in August 2001,[9] the Bush administration restricted federal funding only to research on a limited number of previously existing human embryonic stem cell lines; on March 9, 2009, President Obama formally lifted that funding restriction.[10] At this writing, it seems likely that federal funding will begin to flow toward broader embryonic stem cell research in only a few months. Pursuant to the Dickey-Wicker Amendment, the federal government has been prohibited annually from funding the cloning or destruction of any human embryo,[11] but that amendment has been construed as permitting federal funding for subsequent research on cell lines created from embryos cloned or destroyed with non-federal funds.

States and private organizations have also taken a central role in funding embryonic stem cell research. Aside from a few states that impose more restrictive laws, both embryonic research and human cloning for research

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9. For the full text of President Bush's speech on human embryonic stem cell research, see Press Release, Office of the Press Secretary, White House, President Discusses Stem Cell Research (Aug. 9, 2001), *available at* http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html.

10. *See* Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

11. The Dickey (or Dickey-Wicker) Amendment is actually a rider that Congress has attached to the appropriations bill for Health and Human Services annually since 1996. "[T]he Dickey Amendment prohibits federal engagement in a field of research pertaining to the nature of the human embryo, its disorders of development, and the derivation of new human embryonic stem-cell lines." George Q. Daley, *Missed Opportunities in Embryonic Stem-Cell Research*, 351 NEW ENG. J. MED. 627, 628 (2004).

purposes remain permissible in most of the country.[12] Further, taking advantage of the vacuum left by the temporary absence of federal funding, a number of state governments have decided to fund human embryonic stem cell research and cloning.[13] By offering their own funding, those states hope to gain a competitive advantage over unfunded states in university and industry development, while also satisfying disease-group constituencies who were anxious to see stem cell research generate cures. Private money has also flowed generously toward such research; Harvard University's prominent stem cell research program, for example, is mostly funded by private philanthropy.[14]

Although for the moment stem cell research has widespread public appeal and growing support from the federal government, states, and private institutions, there is reason to believe that this broad consensus will not be terribly stable. The funding and methods of stem cell research have generated a new round of debates, and underlying moral questions regarding the status of the embryo are far from resolved. The public's support for embryonic stem cell research seems not to be concentrated at the stable ends of the above tripartite division of arguments. When asked blankly whether they support or oppose stem cell research, a substantial majority of Americans say they support it.[15] But that apparent support erodes considerably when the question stresses that the research involves the destruction of human embryos.[16] Support increases, however, when the question instead highlights the high human and economic costs of the diseases that stem cell research might one day treat or cure.[17] In light of this rather confused and confusing data, it seems reasonable to conclude that a sizeable chunk of Americans take a moral balancing approach, namely the third view listed above. This moral balancing approach leads to different conclusions when the weights on different sides of the scale (embryonic destruction and research potential) are called to attention. At the moment, most of the public seems to have resolved the balance in favor of research, if it has resolved the conflict at all. But if anything occurred to alter its perception of the weight either

12. For a periodically updated chart summarizing state laws governing the treatment of fetuses and embryos in research, see National Conference of State Legislatures, Stem Cell Research, http://www.ncsl.org/programs/health/Genetics/embfet.htm (last visited Apr. 21, 2009).

13. States currently funding embryonic stem cell research include California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York, and Ohio. *See id.*

14. *See* Harvard Stem Cell Institute, Frequently Asked Questions, http://www.hsci.harvard.edu/faq#FAQ14 (last visited Apr. 21, 2009) ("HSCI is supported primarily by private philanthropic donations.").

15. Yuval Levin, *Public Opinion and the Embryo Debates*, 20 NEW ATLANTIS 47, 50 (2008).

16. *Compare id.* (showing that 69% of people surveyed supported stem cell research) *with id.* at 52 (finding that only 33% of people believed an embryo should be destroyed for scientific or research purposes).

17. *Id.* at 52 (finding that 54% of people surveyed agreed that the economic and personal costs of disease are greater than the risks associated with the destruction of embryos).

on the research-progress side of the scale or on the moral status side, the existing consensus could easily shift.

To be sure, a new round of debate on stem cell and cloning research is not apt to culminate in either a wholesale reversal or a solid reaffirmation of the core position about the moral permissibility of human embryonic stem cell and cloning research. The next debates are likely, instead, to have decentralized and seemingly marginal effects. As different groups find their moral balances shifting, some funding may be expanded or cut; particular research techniques may be banned while others are underwritten; priorities will shift; the caché of different research programs and institutions may be evaluated differently. Collectively, these dozens of small and decentralized political and financial adjustments could enhance the research, hinder it, or dramatically alter its scope and quality.

The Articles in this book are ideal reading material for someone who wants to follow and understand the significance of these new debates.

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One thing that will not change is the urgent desire of many Americans for the development of cures for devastating diseases. That urgent desire made itself known throughout the first national debate; every state that considered funding stem cell research heard impassioned pleas from mothers of diabetic children, from men dying of Parkinson's disease, and from Alzheimer's caregivers.

But urgent desires can lead to unrealistic expectations, and unrealistic expectations easily lead to disappointment. There is strong evidence that expectations for stem cell research are already unjustifiably high. Recent polls suggest that nearly a third of Americans believe, incorrectly, that embryonic stem cell research has already delivered usable cures or treatments for human disease.[18] And this incorrect belief is more common among those who claim some familiarity with the stem cell research issue![19] Many more people expect or demand cures soon. At a recent public meeting of Connecticut's Stem Cell Research Advisory Committee—at which the committee was reviewing one-year progress reports from university investigators who had received research grants in the first round of state funding—the leader of the state chapter of a national spinal-injury lobby group spoke of his disappointment that researchers were not yet making progress toward cures.[20] He spoke also of his own personal desire to

18. *Id.* at 44.

19. *Id.* (noting that 40% of those who claimed to have some knowledge about the research believed, incorrectly, that embryonic stem cells had yielded therapeutic results, compared to only 23% of those who said they were unfamiliar with the research).

20. David Meneker, Remarks at the Meeting of the Connecticut Stem Cell Research Advisory Committee 141 (May 20, 2008) (transcript available at http://www.ct.gov/dph/lib/

rise one day and walk away from his wheelchair.[21] Such high hopes may easily be dashed—and if they are, stem cell research may be abandoned by some of those who were originally its greatest supporters.

From where did those high hopes come? **Daniel Callahan** argues that the stem cell research "juggernaut" was the deliberate creation of a coordinated public relations campaign. That campaign, he argues, hyped research potential and then used that hype to undergird a supposed "moral obligation" to conduct the research.

Researchers have been enthusiastic and optimistic about therapeutic research programs before. For a dose of humility, we need only remember the hype surrounding gene therapy a few decades ago. In the 1980s, even those who opposed gene therapy took it for granted that it would radically alter medicine; indeed, their primary objections were based on the assumption of its success.[22] Gene therapy was thought dangerous precisely because it was going to be too powerful, that it was going to transform us into eugenicists or demigods, altering our genes and our gene pool before we had thought carefully about the results. Today, gene therapy is still in its infancy. Only a handful of therapies have ever been tested in humans, and in more than one high-profile case, that testing has resulted in the deaths of research subjects.[23] It may well be that the development of stem cell cures will take longer, much longer, than many of its proponents anticipate. There may be dramatic bumps in the road—bumps that cause substantial delay and disappointed expectations. This could turn the tide against stem cell research, or at least against public funding for it.

Jane Maienschein is concerned with a different and more subtle sort of hype that pervades the national debate on stem cell research. That debate, she laments, is comprehensively polluted by an idea of genetic determinism inspired

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dph/Transcript_5-20-08.doc). I attended this meeting and heard these comments as a member of the Connecticut Stem Cell Research Advisory Committee.

21. *Id.*

22. *See, e.g.*, Clifford Grobstein & Michael Flower, *Gene Therapy: Proceed with Caution*, HASTINGS CENTER REP., Apr. 1984, at 13.

23. For a brief summary of the current status of gene therapy research, including summary discussion of some of its major setbacks, see Human Genome Project Information, Gene Therapy, http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml (last visited Apr. 21, 2009). For an extensive review of the case of Jesse Gelsinger, who died during a gene transfer experiment at the University of Pennsylvania, see Robert Steinbrook, *The Gelsinger Case*, *in* THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 110 (Ezekiel J. Emanuel et al. eds., 2008). *See also* Jocelyn Kaiser, *Gene Transfer an Unlikely Contributor to Patient's Death*, 318 SCIENCE 1535, 1535 (2007) (describing an investigation into the death of a gene therapy trial participant, which "concluded that the gene transfer was unlikely to have contributed . . . but that this 'cannot definitively be ruled out'") (citations omitted); *Panel Urges Limits on X-SCID Trials*, 307 SCIENCE 1544, 1544 (2005) (noting the death of one child during a gene therapy trial for immunodeficiency disease in France).

by earlier debates about cloning and by the well-publicized Human Genome Project. The basic view that our genetic structure is the core of our being, and that we do and become what our genes command, is pervasive even among scientists—and yet, Maienschein argues, this view is importantly incorrect. Maienschein, a historian and philosopher of biology, shows us how this view obtained its cultural authority and how it is that the biology with which the public is most familiar is a limited biology of genetic determinism. She then makes some recommendations for the conduct of a more scientifically informed debate about cloning and human development going forward.

If one danger to the current stem cell consensus comes from disappointed expectations in the research, a second danger comes from dramatic new progress in that research. Key arguments in the debate about embryonic stem cell research concern the availability of alternative means to create cell lines that would be as useful as embryonic cells—means that might bypass the core ethical debate because they do not involve the creation or destruction of human embryos. If scientists could only find an adequate substitute (or a set of adequate substitutes) for embryonic stem cells, then the entire stem cell research program could proceed without the moral worries about embryo destruction and therapeutic cloning. In the past, opponents of embryonic stem cell research argued that adult stem cell research was a fully adequate substitute for embryonic stem cell research, and indeed that adult stem cells held greater therapeutic promise. Few scientists were willing to concede this, however, given the comparatively limited ability of adult stem cells to differentiate and the difficulties of culturing adequate numbers of adult cells for research. Some argued, also, that the opponents of embryonic stem cell research were over-hyping the therapeutic potential of adult stem cells. In a different effort to square the ethical circle, William Hurlbut of the President's Council for Bioethics argued for the creation of a "biological artifact," a kind of deliberately "disabled" embryo that was incapable of developing into a human being, specifically because it had been engineered to lack the capacity to generate a placenta.[24] Since destruction of such an embryo would not involve the destruction of a potential human being, Hurlbut reasoned, the ethical problem would be solved. Critics pointed out, however, that the creation of the "disabled" embryo would itself involve the destruction of an embryo.

But in the past few years, stem cell science has progressed considerably, and there are more, and perhaps more realistic, alternatives to embryonic stem cell and cloning research in the offing. Most dramatically, in 2007, scientists in the

24. For a detailed discussion of Hurlbut's proposal, see PRESIDENT'S COUNCIL ON BIOETHICS, ALTERNATIVE SOURCES OF HUMAN PLURIPOTENT STEM CELLS: A WHITE PAPER 36-50 (2005), *available at* http://www.bioethics.gov/reports/white_paper/alternative_sources_white_paper.pdf.

United States[25] and Japan[26] demonstrated their ability to use viruses to introduce certain changes in the genetic content and expression of specialized somatic (adult) cells, rendering them pluripotent (able to differentiate into different specialized cells), in a manner similar to embryonic stem cells. In 2008, similar "induced pluripotency" was achieved in mice without the use of the viral vectors.[27] Induced pluripotency is not yet a real substitute for embryonic stem cell research because the exact mechanism by which pluripotency is induced is imperfectly understood even by the researchers. It also remains unclear whether induced pluripotent stem cells will share identical characteristics with their embryonic counterparts. But there is considerable potential here for doing research on cell specialization without embryonic destruction. **Rajesh Rao** reviews this and a host of other potential substitutes for embryonic stem cell and cloning research, including parthenogenesis (which involves the development of stem cells from an unfertilized egg) and cellular reprogramming via cell fusion and other techniques.

For many, the moral permissibility of embryonic destruction in research turns on the idea that the embryos being destroyed "would have been destroyed anyway." The question of using "spare" embryos from assisted reproduction is returning to the forefront of the debate for a number of different and mutually reinforcing reasons. First, the Roman Catholic Church has recently released a formal instruction on bioethics, which comprehensively opposes assisted reproduction, the creation of supernumerary embryos, and the use of such embryos in research.[28] Second, recent scholarship has questioned the quality of consent given by infertile couples who permit their "spare" embryos to be used in research: one scholar has revealed that some of the federally fundable stem cell lines were secured with inadequate parental consent;[29] other scholars have questioned the propriety of asking couples to consent to research use of their embryos at the same time as, and in the same document as, their consent to fertility treatment;[30] and others have questioned whether the burdens of non-

25. Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917 (2007).

26. Kazutoshi Takahashi, *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861 (2007).

27. Keisuke Okita et. al., *Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vectors,* 322 SCIENCE 949; *see also* Matthias Stadtfeld et al., *Induced Pluripotent Stem Cells Generated Without Viral Integration*, 322 SCIENCE 945 (2008).

28. CONGREGATION FOR THE DOCTRINE OF THE FAITH, INSTRUCTION *DIGNITAS PERSONAE* ON CERTAIN BIOETHICAL QUESTIONS (2008), *available at* http://www.usccb.org/comm/Dignitaspersonae/Dignitas_Personae.pdf.

29. *See, e.g.*, Robert Streiffer, *Informed Consent and Federal Funding for Stem Cell Research*, HASTINGS CENTER REP., May-June 2008, at 40.

30. *See, e.g.*, Ellen A. Waldman, *Disputing Over Embryos: Of Contracts and Consents*, 32 ARIZ. ST. L.J. 897, 918-32 (2000).

fertility-related stem cell research should fall solely upon infertile couples.[31] Given this kind of debate, state legislatures will likely be revisiting the question of the provenance of research embryos.[32] **Gene Outka**'s Article is a sophisticated philosophical defense of the use of "spare" embryos in research, based on the principle that "nothing is lost."[33] The latter part of **Daniel Callahan**'s paper effectively engages Outka in debate on this point, rejecting the "nothing is lost" principle.

State and federal legislatures have repeatedly flirted with some sort of ban on reproductive and/or therapeutic cloning—not always sharply distinguishing between the two. Calls for such legislation have followed closely on the heels of disclosures by scientists that they have succeeded in cloning human embryos for therapeutic purposes. **Robert Burt**'s paper takes a look at the possible constitutional limits of any effort to regulate or ban research cloning. His analysis examines a number of challenges to such a ban, including a possible constitutional right to free scientific inquiry; a claim that such regulation might interfere unconstitutionally with couples' reproductive freedom; a claim that executive branch restrictions on research funding might be unconstitutional; and the claim that only states, and not the federal government, have constitutional authority to regulate in this area.

Robert Levine offers a critical view of the Bush administration's research funding policy and an argument for expanded federal regulation of federally funded stem cell research. In Levine's view, the federal refusal to fund embryonic stem cell research, but to permit it to proceed with private funding, was a political cop-out, a way to appear to satisfy parties on both sides of a tough moral question. But the politically safe decision to permit research to proceed without government funding may have had negative collateral consequences for research subjects. Funding, Levine argues, has commonly come hand-in-hand with regulatory oversight and protections for research subjects. He illustrates his point by comparing stem cell research with federal regulations governing the oversight of research on human subjects, and with the largely privately funded, and largely unregulated, field of assisted reproductive technology. He offers some timely recommendations for federal regulation of stem cell research, which will take on increasing importance as funding restrictions lessen.

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31. *See, e.g.*, Angela Ballantyne & Sheryl de Lacey, *Wanted—Egg Donors for Research: A Research Ethics Approach to Donor Recruitment and Compensation*, 1 INT'L J. FEMINIST APPROACHES TO BIOETHICS 145 (2008).

32. The NIH has also recently considered the sources of embryos used in research. *See* Draft National Institutes of Health Guidelines for Human Stem Cell Research Notice, 74 Fed. Reg. 18,578 (proposed Apr. 23, 2009)

33. This is an updated version of the argument that he first presented in a discussion paper before the President's Council on Bioethics.

Finally, **James Fossett**'s Article shifts the focus away from federal policy in the embryonic stem cell and cloning area, and toward the question of state and private funding for that research under the new administration. Fossett summarizes the roles of state governments and private philanthropies in funding stem cell research, and predicts that, though the federal government may move to fund more embryonic stem cell research, major federal funding is unlikely. He predicts, also, that the advent of such funding will do little to diminish the state's role in sponsoring and regulating embryonic stem cell research. He argues that robust federalism is not only desirable, but necessary, in this research sector.

Taken together, these Articles offer a thorough and up-to-date overview of the fields of embryonic stem cell and cloning science, ethics, and policy.

Constitutional Constraints on the Regulation of Cloning

Robert A. Burt*

In 1995, Congress enacted a ban on federal funding for experimentation with human embryos.[1] In 2001, President George W. Bush issued a presidential policy statement extending this funding ban to research on human stem cells extracted from embryos except for research on a limited number of cell lines that had previously been established;[2] he reiterated this position in a 2007 executive order.[3] In his 2008 presidential campaign, Barack Obama promised to support stem cell research.[4] It now seems likely that in addition to rescinding Bush's executive order,[5] Obama will ask Congress to repeal its funding ban from 1995, which still prohibits scientists from generating new stem cell lines.[6]

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1. Known as the Dickey-Wicker Amendment, this ban was formally a rider to federal appropriations for Labor, Health and Human Services, and Education; it has been renewed every year since 1996. Balanced Budget Downpayment Act, Pub. L. No. 104-99 § 128, 110 Stat. 26, 34 (1996); *see* Sheryl Gay Stolberg, *New Stem Cell Policy To Leave Thorniest Issue to Congress*, N.Y. TIMES, Mar. 9, 2009, at A1.

2. Press Release, Office of the Press Secretary, White House, President Discusses Stem Cell Research (Aug. 9, 2001), *available at* http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html.

3. Exec. Order No. 13,435, 72 Fed. Reg. 34,591 (June 22, 2007).

4. *See, e.g.*, Barack Obama & Joe Biden, The Change We Need, Technology, http://www.barackobama.com/issues/technology/ (last visited Mar. 25, 2009).

5. Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009); *see also* White House Press Office, Fact Sheet on Presidential Executive Order: Removing Barriers to Responsible Scientific Research Involving Human Stem Cells, http://www.whitehouse.gov/the_press_office/Fact-Sheet-on-Presidential-Executive-Order (last visited Mar. 25, 2009).

6. *See* Stolberg, *supra* note 1; CNN, CNN's John King Interviews President-Elect Barack Obama, Jan. 16, 2009, http://news.turner.com/article_display.cfm?article_id=4209 ("Well, if we can do something legislative then I usually prefer a legislative process because those are the people's representatives. And I think that on embryonic stem cell research, the fact that you have a bipartisan support around that issue . . . I think that sends a powerful message . . . . I like the idea of the American people's representatives expressing their views on an issue like this.").

The politics surrounding this research could shift again—as the ethical issues of stem cell research are reopened, some critics may promote a total prohibition of human embryonic and stem cell research. Public debate on this issue has thus far focused on policy concerns. The purpose of this Article is to explore constitutional arguments that might be invoked to overturn any federal or state restrictions on human embryonic stem cell research.

Broadly speaking, I will evaluate four different constitutional challenges to a total ban: 1) that such regulations violate researchers' constitutional right of free scientific inquiry; 2) that such regulations violate individual rights to reproductive freedom; 3) that the former Executive Branch restriction imposed an unconstitutional condition on the availability of government funding; and 4) that neither reproductive nor therapeutic cloning is a permissible subject for congressional enactment, but that both are reserved exclusively for state regulatory authority. Exhaustively evaluating these four possible constitutional objections would require writing at least a small textbook on constitutional law; I will instead be suggestive rather than exhaustive.

I. THE RIGHT OF FREE SCIENTIFIC INQUIRY

The First Amendment proscription that Congress "shall make no law . . . abridging the freedom of speech"[7] might seem an obvious haven for scientific researchers committed to intellectual inquiry into the basic workings of the human organism. On at least a few occasions, the Supreme Court has clearly asserted that freedom of speech applies not just to expression but also to teaching and intellectual inquiry that could lead to expression.[8] In its most expansive

7. U.S. CONST. amend. I.

8. *See, e.g.*, Stanley v. Georgia, 394 U.S. 557, 564, 567 (1969) (striking down a Georgia law forbidding the possession of obscene material, noting that the "right to receive information and ideas, regardless of their social worth, . . . is fundamental to our free society," and that "the State may no more prohibit mere possession of obscene matter on the ground that it may lead to antisocial conduct than it may prohibit possession of chemistry books on the ground that they may lead to the manufacture of homemade spirits"); Keyishian v. Bd. of Regents, 385 U.S. 589, 591-92, 603 (1967) (considering a First Amendment challenge to a New York law requiring teachers to answer questions about membership in the Communist Party); Sweezy v. New Hampshire, 354 U.S. 234, 236, 250 (1957) (plurality decision holding that a professor's academic freedom is infringed when he is compelled to answer questions about a lecture dealing with communism). *But see* Zemel v. Rusk, 381 U.S. 1, 13-17 (1965) (upholding restrictions on citizen travel to Cuba despite a citizen's stated purpose of gathering information about Cuban life and noting that "[t]he right to speak and publish does not carry with it the unrestrained right to gather information"); Steve Keane, *The Case Against Blanket First Amendment Protection of Scientific Research: Articulating a More Limited Scope of Protection*, 59 STAN. L. REV. 505, 528-531 (2006) (rejecting the theory that scientific research should receive First Amendment protection simply because it is a

embrace of this ideal, the Court in 1967 extolled free academic inquiry as a "transcendent value" forbidding "laws that cast a pall of orthodoxy over the classroom."[9] Similarly, in 1957 the Court stated as follows:

> To impose any strait jacket upon the intellectual leaders in our colleges and universities would imperil the future of our Nation. No field of education is so thoroughly comprehended by man that new discoveries cannot yet be made. . . . Teachers and students must always remain free to inquire, to study and to evaluate, to gain new maturity and understanding; otherwise our civilization will stagnate and die.[10]

It is a seemingly easy step to apply these encomia to the pursuit of scientific knowledge in research laboratories, and it is a tempting step beyond that to assert that the current or proposed restrictions on reproductive and research cloning are nothing more than a (forbidden) "pall of orthodoxy" over free-ranging scientific inquiry.

The constitutional argument is, however, not so easy to sustain. The courts have in fact been very sparing in giving any enforceable content to these high-flown dicta.[11] Consider the cases in which individual researchers have claimed that state university officials "cast a pall of orthodoxy" over their free scientific inquiry by dismissing them from employment or removing them from classroom teaching based on the content of their expressed views.[12] The First Amendment

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"precondition" of speech). The Court has also acknowledged the right of the organized press to "gather news." *See, e.g.*, Globe Newspaper Co. v. Superior Court, 457 U.S. 596 (1982) (overturning a Massachusetts law excluding the press from court during testimony of minor sex victims); Richmond Newspapers, Inc. v. Virginia, 448 U.S. 555 (1980) (holding that an order closing a criminal trial infringed the First Amendment right to attend criminal trials); Branzburg v. Hayes, 408 U.S. 665, 681 (1972) ("[W]ithout some protection for seeking out the news, freedom of the press could be eviscerated."). *See generally* Barry P. McDonald, *Government Regulation or Other "Abridgements" of Scientific Research: The Proper Scope of Judicial Review Under the First Amendment,* 54 EMORY L.J. 979, 1053-54 (2005) (using different modes of constitutional reasoning to assess how the First Amendment may protect scientific inquiry, and noting that press-oriented cases may not apply to the gathering of information through scientific inquiry because much scientific research is performed without publication as a primary goal).

9. *Keyishian*, 385 U.S. at 603.

10. *Sweezy*, 354 U.S. at 250.

11. *See generally* J. Peter Byrne, *Academic Freedom: "A Special Concern of the First Amendment,"* 99 YALE L.J. 251, 255 (1989) (arguing that "constitutional academic freedom should primarily insulate the university in core academic affairs from interference by the state").

12. *See, e.g.*, Wozniak v. Conry, 236 F.3d 888, 891 (7th Cir. 2001) (upholding summary judgment where a university stripped a professor of privileges when he refused to submit grading materials and finding that "[n]o person has a fundamental right to teach undergraduate engineering classes without following the university's grading rules"); Bonnell v. Lorenzo, 241 F.3d 800 (6th

would clearly be violated if state officials removed political candidates from the ballot based on substantive objections to the content of their campaign literature, but substantive review by tenure committees in state (as well as private) universities is a well-accepted method of scientific quality control. The First Amendment thus cannot be applied with the same free-ranging breadth in academic or scientific pursuits as in other social endeavors. Moreover, the courts have not been particularly searching or welcoming in any effort to translate this supposed "transcendent value" of free academic inquiry into a coherent and enforceable protection.

A different tack for future doctrinal development might be imagined. Freedom of intellectual inquiry might be conceived not as an individual researcher's right, but as a right of the scientific or academic community—a right based on a recognition of the special characteristic of "scientific truth" as based on communal standards of scientific self-regulation. This conception of scientific truth would be transgressed by restrictions imposed by government officials guided by non-scientific criteria. This formulation would, however, run up against some considerable difficulties of application. Officials clearly have authority to refuse funds for scientific research based on the decidedly non-scientific criterion that other demands on government resources should have higher priority; this difficulty might be addressed, however, by specially permissive rules for restrictions on government funding.[13]

With this proviso, a challenge might be launched against the proposed ban on all (not just federally funded) research or reproductive cloning based on non-scientific criteria about denigrating the "human status" of the cloned organism. But here too the principled basis for such challenge immediately becomes cloudy. For reproductive cloning, there is a respectable body of scientific literature suggesting that there may be substantial (or at least unknown) risks for the long-range health status of the cloned person.[14] This basis for prohibiting

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Cir. 2001) (upholding a teacher's suspension for using offensive language in class when it was not germane to the subject matter and citing similar cases from other jurisdictions); Urofsky v. Gilmore, 216 F.3d 401 (4th Cir. 2000) (upholding a state statute restricting the ability of state employees to access sexually explicit material as applied to public university professors and characterizing academic freedom as inhering in universities, not in individual professors); Edwards v. Cal. Univ. of Pa., 156 F.3d 488, 491 (3rd Cir. 1998) (finding that the First Amendment does not grant the professor the right to select curriculum materials that contravened university policy and noting that "a public university professor does not have a First Amendment right to decide what will be taught in the classroom"). *But see* Hardy v. Jefferson Cmty. Coll., 260 F.3d 671, 680 (6th Cir. 2001) (finding that refusal to renew a teaching contract based on in-class speech could violate the First Amendment and noting that "a teacher's in-class speech deserves constitutional protection").

13. *See infra* Part III.

14. *See generally* IRVING L. WEISSMAN, SCIENTIFIC AND MEDICAL ASPECTS OF HUMAN

reproductive cloning might appear well within "scientific criteria." But is it clear that other objections to reproductive cloning, based on humanistic values such as respect for individuality, should be barred from public protection? Is it clear that professional exponents of "science" should be given exclusive social authority for deciding our collective futures? To assert that only "scientific" criteria might guide social regulation is to beg the ultimate question at issue: what is the proper role of science and scientists in shaping the values of our shared social life?

The First Amendment, in its commitment to wide-open, robust inquiry, does not answer this question; it demands that the answer be openly and endlessly debated. Scientists cannot, therefore, claim its protection on the basis that their self-regulated community is the sole repository of "truth" about any contestable issue regarding our social life; that claim, in itself, is antithetical to the underlying value of the First Amendment of free speech and inquiry.

II. THE RIGHT TO REPRODUCTIVE FREEDOM

Publicly enacted bans on cloning might be challenged not by their scientific purveyors but by individuals who want to use the technology, whether to reproduce an entire human being or only to produce human embryos by cloning their own cells. This claim could be based on the Supreme Court's decision in *Roe v. Wade*[15] and the line of cases endorsing a constitutional right of "privacy" or "liberty" in controlling one's own reproductive capacities.[16] The principle derived from the abortion cases could clearly apply to an individual's choice to give birth to a child whether the child is conceived by cloning, *in vitro* fertilization or some other methodology. The *Roe* principle could also support the right to refrain from having a child—not just by contraception or abortion, but through other techniques for interrupting fetal development, such as destroying the embryo for research purposes.

Given the way the Supreme Court has developed the *Roe* doctrine in recent years, however, it seems most likely that none of the proposed congressional restrictions on reproductive cloning would be invalidated on individual "privacy" or "liberty" grounds. In 1992, the Court reinterpreted *Roe* by ruling that states were not entirely prohibited from restricting an individual's right to reproductive choice, but instead that states were prohibited only from imposing an "undue

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REPRODUCTIVE CLONING (2002).

15. 410 U.S. 113 (1973).

16. *See* Stenberg v. Carhart, 530 U.S. 914 (2000); Planned Parenthood of Se. Pa. v. Casey, 505 U.S. 833 (1992); Roe v. Wade, 410 U.S. 113 (1973); Eisenstadt v. Baird, 405 U.S. 438 (1972); Griswold v. Connecticut, 381 U.S. 479 (1965); *see also* Skinner v. Oklahoma, 316 U.S. 535, 541 (1942) (enforcing strict scrutiny for review of the classifications used in state sterilization laws because of the "basic liberty" being deprived).

burden."[17] The distinction between impermissible "undue" and permitted "due" burdens is not exactly pellucid in the Court's formulary. It seems likely, however, that prohibition of reproductive cloning in order to protect the health of the cloned child would pass muster under this cloudy standard, whether the health risk is understood as physical or psychological. Even before narrowing its interpretation of *Roe*, the Court had endorsed restrictions on access to drugs to protect all potential users from health risks, although some individuals wanted to forego this protection.[18] Similarly, the Court has subsequently upheld prohibition of physician-assisted suicide even for terminally ill individuals who wanted this course for themselves.[19] If the Court has been willing to uphold restrictions on choices in order to protect individuals from health risks they would themselves accept, there would be no basis for overturning state prohibitions against one individual's inflicting health risks on another (namely, the embryo potentially able to develop into a viable human being) who had expressed no choice in the matter.

In contrast to reproductive cloning, a person's claim for the right to use her cells for research or therapeutic cloning would face a different obstacle. A state prohibition preventing one from using her cells for therapeutic purposes does not seem to present an "undue" burden on the donor because the state is not forcing her to use her body in ways she does not want to (as it does in the case of abortion bans). Instead, prohibition of research or therapeutic cloning might be understood as a restriction on an individual's liberty to do what she pleases with any part of her body, but it is not clear that *Roe* itself endorsed this libertarian premise. (Consider, for example, laws restricting prostitution or drug use, which narrow the claimed liberties on individuals' use of their bodies.) Understanding *Roe* as more concerned with "privacy" than with "liberty" provides a justification for prohibitions against research or therapeutic cloning, which, unlike forcing continuation of pregnancy, regulate events entirely outside the body of the individual cell donor. *Roe* itself, moreover, accepted state regulation of abortion after the fetus was capable of survival outside the mother's body—after the moment of "viability"[20]—and state regulation of the disposition of the viable

17. *Casey*, 505 U.S. at 16.

18. *See* United States v. Rutherford, 442 U.S. 544 (1979) (upholding the FDA's proscription of Laetrile for cancer treatment). The D.C. Circuit recently made a similar holding denying terminally ill cancer patients access to experimental medications that have not been FDA-approved. Abigail Alliance v. von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007), *cert. denied*, 128 S.Ct. 1069 (2008).

19. *See* Vacco v. Quill, 521 U.S. 793 (1997); Washington v. Glucksberg, 521 U.S. 702 (1997).

20. *Roe v. Wade*, 410 U.S. at 163 ("With respect to the State's important and legitimate interest in potential life, the 'compelling' point is at viability. This is so because the fetus then presumably has the capability of meaningful life outside the mother's womb. State regulation protective of fetal life after viability thus has both logical and biological justifications.").

cloned cell would find justification here.

III. UNCONSTITUTIONAL CONDITIONS ON THE AVAILABILITY OF GOVERNMENT FUNDING

With Congressional restrictions still in force at this time,[21] the use of federal funds for reproductive or research cloning outside specific circumstances remains forbidden. If government funding were equated with private philanthropy, it would be difficult to imagine a basis for challenging the government's decision to spend its funds for some purposes but not for others, as it saw fit. In our constitutional scheme, however, the government has obligations that private philanthropists do not; the government is obliged to honor public norms of behavior that private parties are free to avoid. Thus, for example, the Constitution forbids the government from giving funds only to Catholics but not to other religious groups,[22] whereas private parties are free to indulge religious preferences (and, indeed, are constitutionally protected in acting on such preferences under the First Amendment).

Nonetheless, a constitutional argument against federal funding restrictions on cloning for reproductive or research purposes would be unlikely to succeed. The funding restriction cannot be opposed on the ground that potential recipients have an independent constitutional right to engage in cloning; for the reasons already outlined here, it is difficult to see the basis for claiming such a right. Even if there were a constitutional right against government prohibition of cloning, it still would not follow that the federal or state governments are obliged to provide funds for carrying out these activities.

The Supreme Court has clearly set its face against such a ruling in a series of cases where state and federal legislatures forbade the use of public funds in carrying out abortions, or even simply prohibited the funded agency from counseling women about the possibility of obtaining an abortion.[23] These

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21. *See supra* note 1.

22. *See, e.g.*, Lemon v. Kurtzman, 403 U.S. 602 (1971) (holding that to avoid infringing the Establishment Clause, state statutes must have a secular legislative purpose, must not have the primary effect of advancing or inhibiting religion, and must not foster excessive entanglement with religion); *see also* Jane Lampman, *Obama Would Overhaul Bush's Faith-Based Initiatives*, CHRISTIAN SCI. MONITOR, Jul. 2, 2008, http://www.csmonitor.com/2008/0702/p25s10-uspo.html (noting that some watchdog groups have won lawsuits when faith-based groups have used federal funding for religious purposes and describing the restrictions Obama recommends for federal dollars given to faith-based groups).

23. *See, e.g.*, Rust v. Sullivan, 500 U.S. 173 (1991) (upholding congressional prohibition against physicians employed by federally funded agencies from informing women about abortion services); Harris v. McRae, 448 U.S. 297 (1980) (upholding congressional denial of federal Medicaid funds for abortions, even for maternal health protection); Maher v. Roe, 432 U.S. 464

funding restrictions obviously made it more difficult for pregnant women to obtain abortions, but the Court has ruled that public agencies are not obliged to financially subsidize or to provide any measure of support for abortions, even though the agencies may not constitutionally prohibit any woman from obtaining an abortion. If, as I have suggested, governmental restriction of cloning for reproductive or research purposes is not constitutionally prohibited, it is difficult to see the basis for any constitutional challenge to refusal of public funding restrictions for such cloning.

IV. CLONING MAY BE REGULATED ONLY BY STATES AND NOT BY CONGRESS

Just a few years ago, it would have been difficult to imagine a successful argument that states possess exclusive constitutional authority to regulate cloning. Two bases for congressional regulatory authority would have seemed available. One basis could have been found in Section 5 of the Fourteenth Amendment to the Constitution. This section provides that "Congress shall have power to enforce, by appropriate legislation, the provisions" of the Amendment, including its guarantee of equal protection of the laws.[24] In the 1960s, as Congress sought to extend protections against state-supported race and sex discrimination, the Court construed Section 5 authority to permit broader congressional conceptions of equal protection than the Court alone might have been willing to endorse without statutory expansion.[25] By this construction, Congress could readily have justified a conclusion that reproductive cloning harmed the resulting person and thereby infringed his right to equal protection of the laws. Similarly, Congress could have asserted that a cloned embryo was sufficiently endowed with human characteristics that its use for research cloning violated the equal protection guarantee. But this expansive conception of the scope of Congress' Section 5 authority has effectively vanished from the current Court's jurisprudence.[26]

In particular, the Court's recent decision in *United States v. Morrison*[27] has removed any possibility of constitutional authority for congressional regulation of cloning under Section 5 of the Fourteenth Amendment. In the Violence Against Women Act (VAWA), Congress had provided a federal court remedy for

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(1977) (upholding state denial of Medicaid benefits for abortion while covering childbirth expenses).

24. U.S. CONST. amend. XIV, § 5.

25. *See* Katzenbach v. Morgan, 384 U.S. 641 (1966).

26. *See, e.g.*, Robert C. Post & Reva B. Siegel, *Protecting the Constitution from the People: Juricentric Restrictions on Section Five Power*, 78 IND. L.J. 1 (2003) (arguing that the Court's recent Section 5 jurisprudence breaks from decades of deference and reflects an aggressive vision of a "juricentric" Constitution).

27. 529 U.S. 598 (2000).

gender-motivated violence by private actors partly on the ground that state laws in many jurisdictions were inadequate to protect women's safety.[28] The *Morrison* Court ruled, however, that the Fourteenth Amendment applied only to "state action" and not to private conduct, rejecting the congressional rationale that state failure to provide adequate protection against violence to women was, in itself, an adequate basis for finding an equal protection violation by states. By the Court's narrow construction of requisite state action, it is not possible to see how Congress could justify any ban of reproductive or research cloning unless the activity were directly conducted in state-run laboratories. Following *Morrison*, Section 5 of the Fourteenth Amendment provides no authority for congressional regulation of cloning.

The second possible basis for federal regulation of cloning—seemingly even clearer than its Section 5 authority—would have been congressional authority to regulate interstate commerce, as authorized by Article I, Section 8 of the Constitution. Prior to the 1930s, the Supreme Court had narrowly construed this authority to exclude such matters as child labor or coal mining from congressional regulatory authority, even though such activities had clear connections with and substantial impact on interstate commercial activity.[29] The Great Depression and the activist interventions of the New Deal led the Court to abandon its restrictive interpretation of the federal commerce authority and, over the next sixty years, to validate federal regulatory actions with even the most tenuous demonstrable connection with interstate commerce.[30] At the same time, the increasingly complex integration of national economic activity apparently provided a constitutionally sufficient link with interstate commerce for virtually any conceivable federal regulation. If the post-New Deal permissive interpretation still held, finding a requisite connection with interstate commerce to justify federal regulation of reproductive or therapeutic cloning would be a foregone conclusion. A sufficient case would arise simply from the economic competition among laboratories in various states to develop the latest cloning techniques and employ the most innovative research scientists—not to mention the interstate transportation of paraphernalia for the cloning activity itself. But the post-New Deal permissiveness is increasingly under challenge by the contemporary Supreme Court.

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28. Violence Against Women Act of 1994, 108 Stat. 1796, 1902, 1941-42 (codified as amended at 42 U.S.C. § 13981 (2000)).

29. *See, e.g.*, Carter v. Carter Coal Co., 298 U.S. 238 (1936); Schechter Poultry Corp. v. United States, 295 U.S. 495 (1935); Hammer v. Dagenhart, 247 U.S. 251 (1918).

30. *See, e.g.*, Katzenbach v. McClung, 379 U.S. 294 (1964); Wickard v. Filburn, 317 U.S. 111 (1942); United States v. Darby, 312 U.S. 100 (1941); United States v. Carolene Products Co., 304 U.S. 144 (1938); NLRB v. Jones & Laughlin Steel Corp., 301 U.S. 1 (1937); West Coast Hotel Co. v. Parrish, 300 U.S. 379 (1937).

The Court's recent decision in *Morrison* appears to undermine any Commerce Clause justification for federal regulatory authority over cloning. In striking down the provision of a federal cause of action for violence against women, *Morrison* dismissed extensive congressional findings that violence against women had substantial impact on interstate commerce because of women's lost hours of employment and increased medical expenses. The Court held that the commerce clause only justified federal regulation of activity which was "economic in nature" rather than "noneconomic . . . conduct [with an] . . . aggregate effect on interstate commerce."[31]

Determining whether cloning is "economic" or "non-economic in nature" is surely a snark hunt, but beneath this foggy concept, the Court appears intent on drawing a constitutional "distinction between what is truly national and what is truly local."[32] Though this "truth" is scarcely less self-evident than the distinction between economic and non-economic conduct, the Court's examples of the "truly local"—that is, "marriage, divorce, and childrearing"[33]—strongly suggest that regulation of cloning would fall on the "truly local" side of the Court's delineation of constitutional authority. Prohibition of reproductive cloning is clearly nothing more than identification of an impermissible technique of "childrearing"; and the destruction of embryos involved in cloning research is based on the progenitor's decision to refrain from childrearing—that is, from carrying embryos to term. There may be other rationales for congressional restrictions—for example, to protect nationwide threats to "the sanctity of embryonic life." But if the Court is intent on constructing a protected area of state hegemony over "non-economic activity" and if childrearing is one defining characteristic of this hegemonic realm, the Court will ignore other characterizations of cloning just as it ignored the economic consequences of gender-based violence in its eagerness to give narrow definition to congressional Commerce Clause authority.

The Court's rediscovery of the constitutional imperative to protect state regulatory autonomy against federal encroachment has thus far been applied to strike down congressional enactments of a liberal stripe; in addition to the Violence Against Women Act, the Court has invoked state-autonomy concerns to overturn federal laws restricting gun possession near school premises[34] and federal protections against age or disability-based discriminations in state government employment.[35]

In its most recent decision, a Court majority appeared to pull back from this

31. *Morrison*, 529 U.S. at 613, 617.

32. *Id.* at 617-18.

33. *Id.* at 616.

34. United States v. Lopez, 514 U.S. 549 (1995).

35. Bd. of Trs. of Univ. of Ala. v. Garrett, 531 U.S. 356 (2001).

enterprise of constraining congressional authority. In *Gonzales v. Raich*,[36] upholding congressional preemption of state laws that permitted the "medical use" of marijuana, the Court insisted that the new state-autonomy cases were limited exceptions that must be read in "the larger context of modern-era Commerce Clause jurisprudence preserved by these cases."[37] Three Justices, however, strenuously dissented from this ruling. The question of the existence and reach of a resuscitated state-autonomy principle thus remains open to dispute.

If, notwithstanding the contrary indication of *Gonzales v. Raich*, the Court persists in refurbishing state autonomy limitations on congressional power, that principle must be sauce for right-wing geese as well as left-wing ganders. If any future Congress were to enact cloning restrictions, the Court should apply its new-found respect for state autonomy with evenhanded consistency. In my view, virtue as well as consistency would support this application. As fuzzy as the line might be for distinguishing the "truly national" from the "truly local" or "economic" conduct from "non-economic" conduct, it is important to protect institutional structures for public deliberation about deeply contentious moral convictions that promote respect for diversity of views and ensure that none of the combatants in these divisive issues can be easily silenced. The moral values at stake in deliberating an issue such as the propriety of reproductive or research cloning are complex and incommensurate. Conclusive resolution of this issue by Congress—a single, national body acting definitively at one moment in time—fails to give adequate respect to the complexity and diversity of the moral perspectives at stake. Unlike other morally contentious matters, cloning research presents no obvious need for the adoption of a singleminded national resolution of whether reproductive or research cloning should go forward. Notwithstanding that some people would prefer a uniform national resolution either for or against cloning, the fact is that local variations on this issue are conceivable—and the Court should seize on this fact in order to promote the democratic values of pluralism.

This issue should be conclusively resolved only by successive actions of state legislatures, necessarily deliberating at different times and responding to different constellations of constituents. This institutional deliberative structure is not only best suited to the specific character of these moral issues, but it is also, and most importantly, a respectful recognition of the diverse character of American society. It may be that, notwithstanding this diversity, a nationally uniform moral position will emerge regarding the moral status of cloning, particularly given recent political events.[38] But we can most reliably assure

36. 545 U.S. 1 (2005).

37. *Id.* at 23.

38. *See supra* notes 5-6.

adequate respect for the currently diverse moral perspectives on this issue by insisting on a multiplicity of deliberative sites and occasions as a requisite path toward the forging of any uniform national view. The actions by various state governments to fund embryonic stem cell research[39] exemplify the workings of a democratic, deliberative process.[40] A blanket Congressional prohibition on such research would dishonor this process. Accordingly, the present and any future Congress should restrain itself or be restrained by the Constitution.

39. *See, e.g.*, James W. Fossett, *Beyond the Low-Hanging Fruit: Stem Cell Research Policy in an Obama Administration*, 9 YALE J. HEALTH POL'Y L. & ETHICS 523 (2009); Kaiser Family Foundation, State Funding of Embryonic & Fetal Research as of January, 2008, http://www.statehealthfacts.org/comparetable.jsp?ind=112&cat=2 (last visited Mar. 25, 2009); Joe Palca, *States Take Lead in Funding Stem-Cell Research* (National Public Radio broadcast, Mar. 30, 2007), *available at* http://www.npr.org/templates/story/story.php?storyId=9244363.

40. *See* Gretchen Ruethling, *Illinois To Pay for Cell Research*, N.Y. TIMES, July 13, 2005, at A17.

Demythologizing the Stem Cell Juggernaut

Daniel Callahan*

The national debate on embryonic stem cells and research cloning has brought out the best and the worst in American culture. The best is on display in many ways. It is a debate that has been marked by an outpouring of sympathy for those suffering from disease or disability or threatened with death. It has drawn on the deep historical reservoir in America of a devotion to research and technological innovation to relieve the human condition. Despite these intensely partisan times, support for the research has easily crossed party lines, among legislators and the public. And it has given hope to perhaps thousands of people suffering from tenacious afflictions and disabilities. Those elements of the debate are impressive and commendable.

Far less commendable were many of the ways in which the campaign in favor of the research was waged to gain money to carry it out. The main focus of this paper is on the early years of the stem cell debate when that effort was most intense. There were, for openers, inflated claims about the value of the research, often in the face of cautions from the researchers themselves. There was also an egregious promotion of what I believe to be an utterly wrong view about a so-called moral obligation to pursue the research. And there was a full display of that most ancient of logical fallacies, the *ad hominem* argument. Many research proponents did not hesitate to label those on the other side as a noxious coalition of right-wing religious fanatics, the fearful, the superstitious, the ignorant, and those invincibly indifferent to human suffering. Some of that kind of rhetoric has been thrown in my direction. The right, sometimes not to be outdone in throwing mud, labeled proponents as enemies of human dignity, who were well down a slippery slope to manufacturing and instrumentalizing human embryos and thus life itself, the crudest kind of utilitarianism.

There may have been bits of truth in each of these stereotypes, but they did not serve well to advance the discussion. There were some larger issues at stake in this conflict, most notably the excessive hype and hyperbole deployed by research supporters, the use of bad arguments, some ethical window-dressing to move the cause along, and a failure to take account of some little-noted but highly relevant facts.

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I confess at the outset that I oppose embryonic stem cell research for either research or human cloning purposes. It is by now evident that I was on the losing team and, as someone who thinks of himself as a liberal, I found myself in the company of many whose values I do not share. I also happen to be pro-choice on abortion, which probably puts me in some odd, idiosyncratic class, maybe a class of one.[1] I will try to reconcile this combination later in the paper.

I most want to demythologize the stem cell juggernaut. The late Protestant theologian Rudolf Bultmann used the term "demythologize" as a way of describing his effort to downplay or altogether deny some key beliefs of Christianity, but without altogether rejecting Christianity. Analogously, I want to deflate the case made for research cloning but not for, say, adult stem cell research (even if it is less "promising"). I use the term "juggernaut" to convey my perception that the force of the research drive, and the public relations work that was invested in it, were remarkable. If it did not persuade President George W. Bush to change his mind, it has otherwise swept away most other opposition. President Barack Obama has already lifted some of the restrictions on the limited use of embryos now in place in government-supported research, although further Congressional action is needed before federal funding may be used in the creation of new cell lines.[2] The fact that many states, some of them facing large budget problems, decided to support the research is just one piece of testimony about the intensity of the enthusiasm. These states include California, Connecticut, Illinois, and Wisconsin.[3]

I. IS THERE A MORAL OBLIGATION TO DO EMBRYONIC STEM CELL RESEARCH?

I begin with the leading candidate for demythologization—the claim that there is some kind of powerful and inescapable moral obligation to carry out the research.

A. Considerations that Weigh Against a Moral Obligation

Well before the stem cell era, the Nobel Laureate Joshua Lederberg once said to me that "the blood of those who will die if biomedical research is not pursued will be upon hands of those who do not support it." Much more recently the distinguished stem cell researcher, Irving Weissman, used almost identical

1. *See* DANIEL CALLAHAN, ABORTION: LAW, CHOICE AND MORALITY (1970).

2. *See* Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009); Sheryl Gay Stolberg, *New Stem Cell Policy To Leave Thorniest Issue to Congress*, N.Y. TIMES, Mar. 9, 2009, at A1; David Stout & Gardiner Harris, *Obama Reversing Stem Cell Limits Imposed by Bush*, N.Y. TIMES, Mar. 7, 2009, at A1, *available at* http://www.nytimes.com/2009/03/07/us/politics/07stem.html.

3. For a listing of state funding, see James W. Fossett, *Beyond the Low-Hanging Fruit: Stem Cell Research Policy in an Obama Administration*, 9 YALE J. HEALTH POL'Y L. & ETHICS 523 (2009).

language on behalf of stem cell research. According to this line of thought, regenerative medicine has the promise and potential of saving millions of lives, afflicted by conditions from heart disease to Alzheimer's, from diabetes to Parkinson's disease. There is said to be a "negative responsibility" for the lives of those that could be lost in the absence of the research.

What a rhetorical club to use—but this claim seems specious and bombastic.[4] I advance three considerations to support my view. The first is that there is a common impression that stem cell research holds out the only hope of curing various prominent diseases—heart disease, diabetes, Alzheimer's and Parkinson's disease, and spinal cord injury. Not so. The National Institutes of Health has invested tens of billions of dollars to cure or ameliorate exactly those same diseases over the years; and it now invests at least $2.8 billion on them each year.[5] The private for-profit sector has invested at least that much as well, and of course each of those diseases has an advocacy group that raises additional research money. Unless we think that the private and public research sectors are simply squandering their money, which no one has said, and unless we believe that none of that ongoing research is "promising" (the most oft-repeated term with stem cell research), then it is simply wrong to assert that the omission of research cloning would amount to an egregious indifference to human suffering.

Many scientists and others say that embryonic stem cell research is the most promising approach. But no one (so far as I know) has even dared to offer statistical probabilities of eventual success, and many are willing to concede that there may never be a dramatically effective clinical application (though they usually add that there will be great gains in basic knowledge).[6] In sum, if there is a moral obligation to do medical research on various deadly diseases, that obligation is already being discharged. To say that the omission of *one* line of research among many others, embryonic stem cell research, constitutes a moral failure of the first magnitude—"blood on our hands"—is insupportable. But it certainly plays well.

The second consideration bears on what economists call "opportunity costs": that is, what else might usefully be done with the money going into stem cell research? At the same time that the $3 billion California referendum was being debated, for instance, the newspapers in that state were reporting that 2.2 million (mainly immigrant) adults were functionally illiterate, almost certainly dooming

4. *See* DANIEL CALLAHAN, WHAT PRICE BETTER HEALTH?: HAZARDS OF THE RESEARCH IMPERATIVE (2003).

5. National Institutes of Health, Research Portfolio Online Reporting Tool (RePORT), Estimates of Funding for Various Research, Condition and Disease Categories (RCDC), http://report.nih.gov/rcdc/categories (last visited Apr. 30, 2009).

6. Nicholas Wade, *Some Scientists See Shift in Stem Cell Hopes*, N.Y. TIMES, Aug. 14, 2006, at A18.

them to poverty, low level jobs, and little upward mobility.[7] The spending of $3 billion on educating them would produce certain and not just promising social benefits, definite and not just speculative community gains—unlike the speculative clinical gains from stem cell research. But no celebrities, leading scientists, biotechnology entrepreneurs, prominent businessmen, or politicians proposed any referendum on that problem. Nor have many of the states initiating stem cell research, sometimes into the hundreds of millions of dollars, been hesitant about simultaneously cutting back on Medicaid benefits, as if the future benefits for future sick people are more important than present benefits for present people.

The third consideration bears on medical progress and medical need. Proponents of the research treat illness and disease as the greatest of threats to human welfare. I would say they are serious harms but by no means the worst facing our society. Even more threatening are the failures to provide insurance for those who do not have it, various forms of inequitable distribution of available resources of many kinds, global warming, racial and immigrant prejudices, poor support of working mothers, and many of the harms that were done to our society by the Bush administration's threats to civil liberties and sensible social priorities.

The developed countries of the world, including the United States, have an average life expectancy (accounting for male and female differences) of about seventy-seven years. This level of life expectancy is perfectly sufficient to sustain generally healthy, economically successful societies. The fact that heart disease (a stem cell target) is our nation's leading killer in no sense entails that it should be considered a major societal problem—unless anything and everything people die from should be considered a national disaster.

In spite of these indicators of disordered priorities, recent conventional research and improved clinical care are, for instance, steadily reducing heart disease mortality. The greatest threat of diabetes does not now come about only from the lack of a cure, but by increasing obesity, a far harder problem to deal with than inadequate treatments. It is also obvious that most of the stem cell target diseases are, save for diabetes and spinal cord injuries, diseases of aging societies, with heart disease, cancer, and increasingly Alzheimer's at the top of the list. Unless we think it an inherent evil that people die in old age, and that nothing less than all-out warfare is required to stamp out diseases that primarily afflict them, then it is reasonable to give a lower research priority to them.

As far as I can make out, the most evil events of the twentieth century came from man's inhumanity to man—world wars, genocide, racial and ethnic

7. Felix Montes & Roy L. Johnson, *The New State of Illiteracy in San Antonio and the Nation*, INTERCULTURAL DEV. RES. ASS'N NEWSL., April 2005, *available at* http://www.idra.org/IDRA_Newsletter/April_2005_Self_-_Renewing_Schools_Reading_and_Literacy/The_New_State_of_Illiteracy_in_San_Antonio_and_in_the_Nation.

violence—not from death by disease, save in poor countries, which are often bereft of research on those tropical and other diseases (such as malaria) that kill them. I believe there is an obligation to carry out research on those tropical diseases as well as HIV/AIDS, which destroys young lives and civic infrastructures in a way far worse than any disease that might be cured or ameliorated by regenerative medicine.

None of the considerations I have offered tell against stem cell research as such, simply against the use of embryos as research material. Adult stem cell research is fine, and if a way can be found to gain embryonic stem cells without destroying embryos that is fine as well. Although I do not believe there is any moral duty to advance the research, to do so could still be considered a human *good*, well worth a public and private investment. But if it is characterized as a good, not an overriding obligation, then it must pass the test of competition and comparison with other goods that need to be pursued for the sake of a better society. What I reject is the high pedestal on which it has been set. For a yet-unproven research possibility, stem cell research does not deserve that honor—though it surely helps to raise money and generate publicity.

B. The Campaign in Support of Stem Cell Research: Origins of a "Moral Duty"

How did embryonic stem cell research get put on such a high pedestal? Historians may someday aptly characterize the drive on behalf of stem cell research as "the perfect PR campaign," one of the best ever waged for medical research. This campaign began in 1998 with a rash of media stories about James Thomson's derivation of the first embryonic stem cell lines from frozen human embryos.[8] Those stem cells, the public was told in often breathless ways, hold the promise of a whole new medical field, that of regenerative medicine, restoring damaged or destroyed cells in many organs of the body.

But it soon became evident that there would be opposition to the research—and particularly against federal support of it—mainly from conservative quarters. At that point the advocates ratcheted up the campaign. Its organizers, led by well-funded research advocacy organizations and various scientific societies, turned to the tried and true methods pioneered in the 1950s by two wealthy philanthropists, Mary Lasker and Florence Mahoney, at that time on behalf of larger appropriations for the National Institutes of Health. Their key tactics were to put together a coalition of prominent scientists, politicians, business people, and celebrities; amass a war chest to pay for publicity; and skillfully use the media.[9] It was a tactic that worked well in the 1950s, and it worked no less well as the

8. James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145 (1998).

9. Elizabeth Brenner Drew, *The Health Syndicate: Washington's Noble Conspirators*, ATLANTIC MONTHLY, Dec. 1967, at 75.

1990s drew to a close and the new millennium arrived. It also had an added touch, which did not hurt. Bush's rejection turned out to be, among Bush critics, an added benefit: if he did not like it, there must have been something going for it.

The Alliance for Aging Research set the tone with its much-cited claim that up to 150 million lives could (and would, and should) be saved if the research was allowed to go forward.[10] Thomas Okarma, CEO of the leading biotechnology firm, Geron, said that "not to develop the technology would do great harm to over 100 million patients in the U.S. alone."[11] A powerful endorsement of the research by dozens of Nobel laureates from all fields of science was publicized,[12] as was a comparable statement of 100 college presidents[13] (most of whom, it is fair to assume, are hardly expert on the subject). Highly supportive public opinion surveys were released, as were enthusiastic declarations by prominent federal senators and representatives. Christopher Reeve, Michael J. Fox, and the journalists Michael Krondack and Michael Kinsley, each the victim of one of the target diseases, played the celebrity role. The National Academy of Sciences and the Institute of Medicine provided glowing endorsements. The media had no trouble finding stories about desperate parents hoping for a cure to their child's diabetes, or spouses taking care of Alzheimer's patients, or paraplegics trapped in wheelchairs. The real estate tycoon behind the push for the California bond initiative, Robert N. Klein, spoke perfectly the inflated language of the national campaign, calling the discovery of the potential of stem cells "one of the great watershed discoveries in history."[14]

It soon became hard to find many in my field, bioethics, who spoke out against the research. As a well-known journalist once asked me, "Why are bioethicists in such lock-step on this issue?" I could think of no answer that would not bring further embarrassment to a field that likes to think of itself as open, evenhanded, and non-partisan. Cynicism greeted the appointment of Leon R. Kass, a longstanding opponent of both reproductive and research cloning, to chair President Bush's Council on Bioethics. That appointment was railed against in the press and in bioethics chat rooms, treated as nothing more than a far-right

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10. *See generally* Alliance for Aging Research, Embryonic Stem Cell Research To Save the Lives of Millions, Spring 2001, http://www.agingresearch.org/content/article/detail/917 (outlining hopes for future stem cell technologies).

11. *See* T. Hviid Nielsen, *10 Years of Stem Cells: What Happened to the Stem Cells?*, 34 J. MED. ETHICS 852, 853 (2008).

12. *See* Rick Weiss, *Nobel Laureates Back Stem Cell Research*, WASH. POST, Feb. 22, 2001, at A2.

13. Tinker Ready, . . . *and ES Cell Strategy*, 7 NATURE MED. 518, 518 (2001) (describing the open letter from college presidents to Health and Human Services Secretary Tommy Thompson).

14. John M. Broder & Andrew Pollack, *Californians To Vote on Spending $3 Billion for Stem Cell Research*, N.Y. TIMES, Sept. 20, 2004, at A23.

move to put an ethical polish on an intolerable, ideology-driven hostility to life-saving research. The columnist Robert Kuttner spoke out against the religious dogmatists standing in the way of the research.[15] No such label is attached to those religious figures who oppose the war in Iraq.

Notably missing from the campaign was any recollection of some earlier advocacy efforts, each accompanied by excitement, hostility toward conservative critics, and unbounded hopes. Well over a decade ago there was a similarly controversial effort to support the implantation of fetal tissue in the brains of Parkinson's patients. It failed, and decisively so. Then there was the effort, beginning around the same time, to test gene therapy as a means of curing disease. That therapy has had meager results and, along the way, claimed the life of a research subject, Jesse Gelsinger.[16] But no letdown seemed quite so striking as that following the completion of the highly touted $3 billion effort to map the human genome, the Human Genome Project. Bill Clinton celebrated the end of that effort by saying it would now be possible to "eradicate once-incurable diseases."[17] Such talk is muted these days. It turns out that there are many fewer human genes than projected, and that in any case proteins—the delivery system for genetic expression—may be more important for medical applications than genes alone. The mantle of eradicating "once-incurable diseases" has now been passed to stem cell research.

There is a scientific response to stories of that kind. Each of the cited failures or disappointments may not, in the long run, turn out to be failures after all. Good science takes time, with many disappointments along the way. The contention that adult stem cells, which can be harvested without embryo destruction, may be as promising as embryonic stem cells regularly draws a brisk response: the embryonic form looks theoretically more promising but, whatever view turns out to be right, good science wants to go down *all* available roads, never knowing in advance which will eventually work best. No doubt that kind of general argument about scientific progress is, historically taken, perfectly true. It is also no less true that it has provided cover for outlandish and improbable scientific promises and possibilities.

I raise the issue of hype, however, not as an argument against the research. Its real harm is that it feeds the notion of a "negative responsibility" or a "moral obligation" to pursue the research. That latter is an argument meant to disarm critics, to overcome ethical objections and resistance, and to characterize opponents as immoral or soft on human suffering. George W. Bush, ironically, must have been reading the same rhetorical playbook by calling the terrorism

15. For an example of this rhetoric, see Robert Kuttner, *When We Trust Science to Religion*, SAN DIEGO UNION-TRIB., Dec. 9, 2001, at G3.

16. Sheryl Gay Stolberg, *The Biotech Death of Jesse Gelsinger*, N.Y. TIMES, Nov. 28, 1999, § 6 (Magazine), at 137.

17. Gail Collins, *Public Interests; A Shot in the Dark*, N.Y. TIMES, June 30, 2000, at A25.

problem a threat to our "national security," and the fight against it a "war." And those who oppose the "war" are, to be sure, labeled as unpatriotic at best and indifferent to the suffering imposed by terrorists at worst.

What about the present case: excessive hype or reasonable hope? The common sense answer is that it is too early to know. But there have been many warning flags along the way, almost always buried at the end of media stories that headline new mouse breakthroughs, further lives to be saved, hopes for support from the new administration, and voices of indignation at the foot-dragging of George W. Bush (for whom, it should be noted, I did not vote). Yet even the most hopeful of scientists have been saying, since 1998, that turning the research promise into useful clinical applications, if possible at all, could take years or even decades to accomplish.

The May 2005 announcement that South Korean researchers had created new lines of embryonic stem cells that, for the first time, carry the genetic signature of diseased or injured patients, and which can be derived in fewer than twenty tries, signaled a great increase in efficiency.[18] It was hailed by other scientists as a dramatic and spectacular advance. Yet it all turned out to be a fraud and an acute embarrassment to the research community. But, if anything, too much was made of it. Fraud has always been present in science. The main importance of the South Korean case was to demonstrate that a well-hyped campaign, with glittering prizes at the end, invites abuse: the greater the prize, the greater the temptation.

Yet at more or less the same time, in June of that year, James Thomson, while continuing to call for federal support of the research, laid out a number of cautions in an interview, in addition to the common scientific reservations about the long time it will take to get any useful clinical results. He said, as the interviewer summarized his comments, "that supporters of stem cell research are overestimating the prospects for transplantation cures, that the current stem-cell lines [and not just those authorized by President Bush, but new ones as well] are not well-suited for such applications anyway, and that there's no need to resort to therapeutic [research] cloning now—or perhaps ever."[19]

While I am not competent to assess his scientific views, it is noteworthy that he had a good word to say for President Bush's compromise position: "[I]t did get the field started, and I think that's a positive way of looking at it."[20] However, he also echoed a frequent criticism of opposition to stem cell research: "[M]ost of the people who oppose this research, and most of those who support this research, do it with a profound amount of misinformation . . . . [Everyone

18. Gretchen Vogel, *Korean Team Speeds Up Creation of Cloned Human Cells*, 309 SCIENCE 1096 (2005).

19. Alan Boyle, *Stem Cell Pioneer Does a Reality Check: James Thomson Reflects on Science and Morality*, MSNBC.COM, June 25, 2005, http://www.msnbc.msn.com/id/8303756.

20. *Id.*

should have] real facts."[21] Well, what should we know? Thompson's interview was interlaced with what he acknowledged to be guesses, uncertain predictions, and varying future scenarios. What facts, if any, would make the prognostication more reliable? For the future of financial and political support, it is important to assess the future of the research. We need to know whether it is a good bet or not, and so far that remains uncertain. There have been, as of 2008, no striking breakthroughs on the clinical front, and the fact that some prominent researchers are now saying that the greatest gain may come from the knowledge generated rather than for the cure of disease may be telling a different story than the one initially advanced. The first clinical trial using cells derived from embryonic stem cells was announced in 2009 (though there was controversy about whether this trial was premature).[22]

It is a fact that a great deal of money and energy, and the best of American public relation and advocacy skills, have been invested in the selling of stem cell research, particularly the embryonic kind. As the California bond drive demonstrated, a combination of biotechnology entrepreneurs, wealthy real estate tycoons, grant-seeking scientists, a muscular governor and other leading politicians, and an eager public have deeper pockets for advocacy than even the Southern California religious right. In the United States, any cause that proclaims improved health and the conquest of disease is usually an easy winner in ideological combat, especially if its cause is pressed with big money and media savvy, and given medical credibility by credentialed experts.

II. EMBRYOS, EMBRYOS, AND MORE EMBRYOS: THEORIES ON THE PERSISTENT DISAGREEMENT OVER THE MORAL STATUS OF THE EMBRYO

I now turn to the moral status of the embryo. For about thirty-five years now I have puzzled and struggled over that status. Some people have sublime and calm self-confidence in the rightness of their views on this issue, and this trait seems to be evenly displayed on the right and left. There is also persistent perplexity on the part of many others—that is, most of us. Wherever one stands, however, it might readily be agreed that there is no end of the disagreement in sight. I have puzzled about why it is hard to achieve consensus. As my wife (pro-life) and I (pro-choice) long ago noted, after decades of argument, we each know all the relevant science and all the relevant moral and philosophical arguments; it is hard to find anyone who can say anything new to either of us. Still, we disagree. I have three theories about this difficulty of overcoming disagreement: one bears on our interests and self-interests, another on our modes of moral analysis, and the third on devising public policy and a regulatory framework for research.

21. *Id.*

22. Andrew Pollack, *Milestone in Research in Stem Cells*, N.Y. TIMES, Jan. 23, 2009, at B1.

A. Interests and Self-Interests

My way of understanding the methodological problems of determining the moral status of the embryo, which has helped me to see why there is no decisive general method of solving problems that mix scientific evidence and moral evaluation, has ineluctably (and sometimes unpleasantly) led me to consider the role played in the process by our interests and self-interests. There are two ways of framing the problem I want to point to. One of them has been to ask why it is that the passions run so high for pro-life and pro-choice advocates in the abortion wars. Each of them has, in my observation, invested their stand with symbolic and policy considerations that go beyond abortion and the moral standing of embryos (or fetuses). Let me call this the "interest" problem: important matters are at stake, bearing on what each side sees as the kind of world in which they want to live, and the only kind of world that anyone should want to live in.

For many feminists, abortion has been a decisive index issue, one whose outcome determines what women's role and social status will be in many areas other than reproduction. If we lose that battle, they have in effect said, we will have lost the war for women's rights. For pro-life advocates, the moral status of embryos and fetuses is no less a decisive index issue, determining how we think of and treat the weakest and most defenseless among us. If we lose this battle, they are saying, we will have lost the war for human dignity. At the extremes, some pro-choice feminists say that the moral status of embryos and fetuses is solely a matter of a woman's decision: they have value insofar as women confer value on them—and that is the kind of absolute power women should have. For their part, some pro-life proponents want abortion, however early the stage, to be understood as nothing less than murder of the innocent, justifying for some violence and non-peaceful protest against those who carry out such atrocities. These attitudes are mainly found at extreme edges of the abortion struggle, but they are less surprising (if not less disturbing) when it is understood that there are larger causes and concerns at stake, of which the moral status of the fetus is the tinderbox, not the whole story.

What I will call the "self-interest" problem raises a number of delicate puzzles. By this I mean the extent to which people, wittingly or unwittingly, allow their self-interest to determine their moral judgments. If my reading of the methodological problem of determining the moral status of the embryo is plausible—we lack any decisive criteria for making a decision—the self-interest issue must consequently raise its head. The way is open, and it is a wide avenue, for the introduction of ideological, political, and self-interested judgments. That is what patently appears to happen.

At least two senses of self-interest can be distinguished. One of them is what might be called acceptable or legitimate self-interest: a minority group seeking an end to discrimination against itself, the disabled lobbying for access to public

facilities, or homeowners seeking the end of industrial pollution practices that threaten their water supply or the health of their children. Each group seeks something of direct benefit to them, perhaps of no particular benefit to the rest of the community, and perhaps even imposing some burdens on everyone else—but it is considered a legitimate claim and a tolerable burden even on those who have nothing special to gain.

But then there is what I will call an ambiguous sense of self-interest, which might be those situations where we at least wonder if the self-interest is crass, that is, where narrowly self-serving desires are at stake. Here we might think of the industrial polluter who knows that there is hazardous pollution that it could well afford to stop. But it persuades itself that the pollution is not all that bad, that nature will eventually take care of it as it biodegrades, and that any serious efforts on its part would endanger its economic strength and thus put at risk the many jobs the community needs. I stress in this example that the company "persuades itself," in order to recognize that most people who display crass self-interest may admit that some self-interest is at stake but not the grossly self-serving kind.

What are we to make of embryonic research scientists who, we assume, must have persuaded themselves that embryos do not have a high enough moral status for concern, and maybe none at all, and thus see no problem in using them for their research? Is it a mere coincidence that, seemingly, only a handful of scientists interested in doing the research appear to have any serious dilemma about using embryos, a far lower proportion than the population as a whole? This can be seen as a classic chicken-egg problem: which came first, their desire to do the research and thus an adaptation of their moral stance toward embryos through self-persuasion; or was there a preexisting stance toward embryos that made it morally tolerable to use them for research?

The same kind of questions can be raised about the lay supporters of the research and particularly those suffering from some disability or life-threatening disease that the research might alleviate. At the least we might say that, for those who want the research to go forward, there are some powerful disincentives against granting embryos so high a status that the research could not proceed. Or, to put it a different way, if the destruction of embryos is understood to be one of balancing their value against that of research benefits, it is not exactly unpredictable that many people will persuade themselves that embryos have a lesser value than those benefits.

I focus on this line of thought because, if science cannot tell us what the moral status of an embryo is, and therefore if the moral values at stake must, so to speak, be imported from the outside, then there is room to seek those moral principles and modes of reasoning most compatible with our other values. If we are as scientists eager to carry out the research, and as patients eager to have its benefits, we will be likely to bring those values to bear on our assessment of

embryos—and to decide against them. But my mode of analysis here cuts two ways: for those who see in various forms of scientific research a threat to human dignity (an important value for their way of life) or the beginning of a slippery slope, they have a powerful incentive to give the embryo a high and inviolable status.

I do not conclude from my line of analysis that the obvious self-interest of either the researchers or their opponents is a matter of crass self-interest; however, I also do not believe that either group is disinterested. The scientific interests of researchers (their notions of the goods to be pursued) are best served by minimizing the moral status of embryos, just as the moral interests of opponents (their notions of the higher goods at stake) are served by maximizing it. What all of this proves to me is that the ambiguous status of the embryo—inescapable since it requires a mode of combined scientific/moral analysis for which we have no good methods—invites and perhaps makes necessary the introduction of values and perspectives drawn from other ways of understanding what we take to be the human good; and these values and perspectives open the way for a self-interested stance. It only gets crass when our own view of what that good might be is utterly self-serving. I do not hesitate to ascribe this judgment to the view of some feminists that the value of the embryo depends entirely on the value a woman chooses to confer upon it, or to politicians who boorishly court conservative support for their election by pandering to pro-embryo forces, treating their enemies as killers.

B. Moral Analysis, Uneasiness, and "Respect": Deriving an "Ought" from an "Is"

There persists a widespread conviction that the answer to the status of the embryo can be found in science. Hence, there are endless debates about the embryological evidence, about whether one can speak of a pre-embryo, about whether human life could someday be derived from a single skin cell, about whether more scientific evidence might one day solve the problem, and so on. But to ask about the moral status or standing of an embryo is an ethical question, and if there was ever an instance when it is not possible logically to derive an *ought* from an *is* (known to philosophers as the naturalistic fallacy), this is it.

Science may eventually be able to empirically explain everything to be known about embryos, their genesis, and their development. But it is beyond the capacity of science to tell us how we ought to treat embryos or evaluate their moral status. That evaluation falls into the category of issues that requires a blend of empirical analysis and moral judgment, but each mode of reasoning draws upon different methods and standards of judgment. To further complicate matters, those different forms of judgment can influence each other: our moral concerns can lead us to look at one among many aspects of the scientific evidence, selecting those that seem relevant (itself a non-scientific judgment),

while the scientific evidence can lead us to reconsider our moral judgments, sometimes whether we like it or not.

Could one conclude from my analysis above that there is nothing more to an evaluation of the moral status of the embryo than our various interests and self-interests at play and manifesting our different views of the good life? There are surely some grounds for thinking so, but there are some reasons to hesitate as well. While there are many research proponents who seem to believe that embryos have no value whatever, they seem to be in the minority. I characterize the stance of many if not most proponents as one of uneasiness, displaying some residual uncertainty about the status of embryos. This uneasiness seems to me to come out in a number of ways: an acknowledgement that, if implanted and not destroyed, embryos have the potential to develop into full persons; a reluctance, other than as a last resort, to create embryos solely for research purposes; an aversion to commercializing the use of embryos, and finally by the adoption of the word "respect" as an apparent effort to find a symbolic compromise characterization of what we owe embryos.

Just what is it that bothers people, even those readily willing to trade off embryos for valuable research? I cannot say for sure, but I suspect that, however much some philosophers may deride the importance of potentiality ("acorns are not oak trees, are they?"), it is hard to entirely put out of our mind and emotions that we all began as embryos; undeniably they are part of everyone's personal history. Even if, as is customary, a distinction is made between the beginning of individual life, on the one hand, and protectable moral standing on the other, that beginning is hard to ignore.

But I can only speculate about the sources of the uneasiness. I want to take a look instead at the word "respect," a much-employed way of placating and domesticating the discomfort. A 1979 report of the Ethics Advisory Board of the Department of Health, Education, and Welfare stated that the early embryo merits "profound respect," though not all "the full legal and moral rights attributed to persons."[23] A 1994 NIH Human Embryo Research Panel said that "the preimplantation human embryo warrants serious moral consideration as a developing form of human life."[24] The National Bioethics Advisory Commission said in 1999 that "human embryos deserve respect as a form of human life."[25]

Since the context of that usage of "respect" is that of the destruction of the embryo, this amounts to what I would call cosmetic ethics. The dictionary

23. Office of the Sec'y, Dep't of Health, Educ., & Welfare, Protection of Human Subjects: HEW Support of In Vitro Fertilization and Embryo Transfer: Report of the Ethics Advisory Board, 44 Fed. Reg. 35,033, at 35,056 (June 18, 1979).

24. 1 NAT'L INST. OF HEALTH, REPORT OF THE HUMAN EMBRYO RESEARCH PANEL, at x (1994), *available at* http://bioethics.gov/reports/past_commissions/human_embryo_vol_1.pdf.

25. 1 NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, at ii (1999), *available at* http://bioethics.georgetown.edu/nbac/stemcell.pdf.

definitions of "respect" appear to leave little room for its use as a balm to the conscience, demanding something more of us than a deferential nod in their direction as they are destroyed strictly for our ends, not their own. Their death is certain, the research results wholly speculative. Try fitting the notion of respect as used by the various commissions into the standard dictionary definitions of respect: "1. To feel or show esteem for; to honor; 2. To show consideration for; avoid violation of; treat with deference."[26]

How can I criticize this symbolic deference paid to embryos and, at the same time, defend the legalization of abortion? In the most defensible abortions, for a serious threat to a woman's health or the certain likelihood of a crippling genetic defect for her embryo or fetus, an abortion can have almost certain beneficial results, at least from the perspective of a woman who believes that it is necessary. Hence, the destruction of the embryo (or, much more likely, a fetus) in that case brings an almost certain benefit to a woman: a life is taken but another life gains, and in that case a life already fully developed gains, not hypothetical future patients who may, in any event, be cured by means of research other than the use of stem cells. I would not want to call the destruction of the embryo or fetus in that case a respectful act, even for a defective fetus. This is still destruction pure and simple, but for very different reasons than clinical research. In short, a different kind of case can be made for abortion, with equally deadly results, than can be made for embryo research. An acceptance of abortion does not entail an acceptance of embryo destruction for research purposes.

C. Public Policy: Embryonic Stem Cell Alternatives, Excess Embryos, and Regulation of Research

I have already tried to make the case that there is no moral obligation to pursue embryonic stem cell research, particularly in light of the vast amount of money already being spent to combat the same conditions at which the research is aimed. Whether the various ideas for deriving stem cells by means other than embryo destruction will succeed is uncertain at this writing, but it would appear to be a worthy goal. That very effort has been challenged on the grounds that there are already thousands of frozen embryos available for research, otherwise to be discarded. That is a tantalizing argument, hard to resist because of its commonsensical nature. Even so, on balance I do resist it, but for a cluster of reasons, not one in particular.

Excess frozen embryos exist as a result of IVF, which in itself seems to me perfectly acceptable. Must less acceptable are the reasons why there are so many frozen embryos available. Most of them come from the treatment of infertile women, but most (though not all) of those women are infertile because of two well-known causes, late procreation and sexually transmitted infection. I would

26. THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE 1107 (1st ed. 1969).

classify excess embryos, then, as a public health problem—yet one that we have medicalized as an inherent biological problem, to be clinically treated rather than the subject of efforts to change the underlying cause (particularly creating social and economic contexts that encourage women to procreate earlier rather than later, in their twenties rather than thirties).[27] Of late, it might be mentioned, efforts are underway to improve IVF to reduce the number of spare embryos, and of course there have been many scientific doubts about whether many or most frozen embryos would be useful anyway.[28] I will not take up here the effort to find ways of gaining stem cells without destroying embryos, but it is an obviously useful effort.

I am not greatly impressed with the argument that spare embryos will be destroyed anyway, and that their use in research is better than simply wasting them. I come to that judgment for a variety of reasons, not one of which is (even to me) fully persuasive in itself, but which add up to a moral gestalt that tilts me against that use: 1) spare embryos need not, and should not exist in the first place—they enhance the chances of an eventual pregnancy, but do not guarantee it, and the recent efforts to reduce their number reflects, at least in part, some level of discomfort; 2) research on dying human beings without their informed consent was once accepted in medical research on the grounds that they were dying anyway and it would be a waste not to make use of them; 3) the one-time (now defrocked) champion of euthanasia, Dr. Kevorkian, contended that the organs of those who were going to suffer capital punishment should routinely be salvaged without their consent because, after all, they were going to be dead soon, and thus would have no further use for their organs and that—clincher of clincher—the salvaged organs could save lives (and Chinese penal authorities have used an identical argument); and 4) the Nazi doctors, who did all kinds of horrible things to concentration camp inmates prior to their certain death in the name of medical research, consoled themselves with the thought of all the medical benefits that could accrue from enlisting the inmates without consent. The research was mainly useful for militarily valuable purposes but at least some seems to have been for saving lives in general. Do we want contemporary medical research placed in such unsavory company? As I said, there is a response to each of the points (we're not Nazis, Chinese penal authorities, or Kevorkian—just good people trying to reduce suffering and death), but their net weight leaves a bad odor in the room, too much for me, at any rate. I would be more impressed with Gene Outka's argument based on a "nothing is lost" principle if I believed it legitimate to have spare embryos, which I do not (it is not medically necessary), and if I believed that there was some obligation to carry out research with embryos, which I do not either. I would argue that "nothing is lost"—to turn

27. *See* REPRO-GEN ETHICS AND THE FUTURE OF GENDER (Frida Simonstein ed., forthcoming June 2009).

28. Gretchen Vogel, *Embryo-Free Techniques Gain Momentum*, 309 SCIENCE 240 (2005).

Outka's argument on its head—by not doing the research at all (as I explained earlier).

CONCLUSION

I conclude with a few observations on the regulation of stem cell research. For at least three decades, the strategy of choice for dealing with morally controversial scientific initiatives which have strong scientific support has been to establish commissions, which propose some limits and then turn the problem over to a regulatory approach. The National Academy of Sciences on stem cell research put together a commission that set forth a number of regulatory ideas (hoping, it appears, to avoid a similar government move), and the state of California as well as some academic research centers have set standards for carrying out the research.[29] But we should not expect commissions and regulations to stop the research. Their purpose is to reduce anxieties about it and to curtail evident abuses. It would be a miracle if any ardent research opponents were appointed members of those commissions or asked to help write the regulations. The aim of the commissions is, after all, to facilitate the research—to make sure it goes forward—but in ways that keep hostile legislators and a worried public at bay.[30] That's the American way, and it well serves those ends, even if at times we pay an ethical price for it. The most important price is that it allows us to keep going with the research but salves our conscience in the process, and it is hardly noticed.

I end my paper with one sentence. The moral status of early embryos is weak and uncertain, but not nearly as weak as the moral status of research cloning.

29. *See* COMM. ON GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH, NAT'L RESEARCH COUNCIL, GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH (2005), *available at* http://www.nap.edu/openbook.php?isbn=0309096537.

30. JOHN H. EVANS, PLAYING GOD? HUMAN GENETIC ENGINEERING AND THE RATIONALIZATION OF PUBLIC BIOETHICAL DEBATE (2002).

Beyond the Low-Hanging Fruit: Stem Cell Research Policy in an Obama Administration

James W. Fossett*

It has been widely expected that the installation of the Obama administration and an expanded Democratic majority in both houses of Congress would produce a major shift in federal human embryonic stem cell (hESC) research policy. During the Bush administration, hESC research was among the most controversial of scientific research topics, and the federal government's role in financing hESC research was limited both in scope and scale. Only certain embryonic stem cell "lines" were eligible for federal research support. Federal regulations prohibited the direct or indirect use of federal funds to finance research using other stem cell lines, so that laboratory space or equipment initially purchased with federal funds, for example, could not be used to support research on ineligible stem cell lines. Congressional attempts either to restrict this research further or to significantly expand the scope and scale of federal support were unsuccessful.

In response to this deadlock in Washington, stem cell advocates turned to state political systems—governors, legislatures, and bureaucracies—to continue pursuing their agendas, with varying degrees of success. These efforts have increased the amount of money devoted to hESC research and established infrastructure—laboratory space, training programs, and the like—that was not subject to federal spending restrictions. While both state and private funding have been adversely affected by the recent recession and the sharp decline in the stock market, states and private donors now spend more money than the federal government to support hESC research.

Many observers expected a major break in the Washington gridlock over stem cell research with the new administration. While a break has occurred, its significance is difficult to assess. President Obama has recently fulfilled his campaign promise to overturn executive orders that limited the scope and scale of federal stem cell funding, but he has also left action on other significant stem cell issues to the National Institutes of Health (NIH) and Congress.

This paper examines the current and likely future funding picture for hESC

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research. It outlines the Bush administration's regulatory and funding policies, inventories current state and private funding for stem cell research, and evaluates the factors likely to shape future stem cell funding. My conclusions are cautionary—while it seems likely that a new administration and Congress may well harvest low-hanging legislative fruit that has already passed Congress by substantial margins, the odds of a major shift in federal stem cell policy, at least in the short run, are low. Many ethical and political issues surrounding stem cell research remain controversial; furthermore, major problems with the national economy, health care, wars in Iraq and Afghanistan, and recent problems in the Middle East seem likely to consume much of the political attention and resources available to both President Obama and Congress. The administration has also committed to positions on other reproductive health issues which may complicate political progress on stem cell questions. The recently enacted economic stimulus package dramatically increases federal spending for biomedical research, but a major increase in stem cell funding seems unlikely. What does seem likely, even if state and private funding for stem cell research decline and federal funding increases, is that most serious policymaking around stem cell research will continue at the state level, rather than relocating to Washington.

I. STEM CELLS—EMBRYONIC AND OTHERS[1]

Stem cell research is a complex scientific and political undertaking in which some aspects are extremely controversial and others are not. In the most general sense, stem cells are undifferentiated "blank" cells that do not have a specific physiological function, but which can, at least in theory, be turned into more specialized cells that perform desired functions. The development of therapies from these cells involves turning them into specialized types of cells that can replace those damaged or destroyed by disease, namely cells that cannot be replaced by natural processes. These specialized cells can then in turn be developed into specialized tissues that can be used in the treatment of disease. If stem cells can be turned into the specialized cells that produce dopamine, for example, they can be used to replace cells that have been damaged by Parkinson's disease.

Stem cell research uses a wide range of these types of cells, and only some of them are controversial. Scientists use a variety of animal stem cells, both embryonic and others, to study disease processes and to experiment with various techniques that may eventually have applications in the treatment of human disease—the techniques that were used to isolate human embryonic stem cells,

1. For a basic overview of stem cell research science, see INT'L SOC'Y FOR STEM CELL RESEARCH, STEM CELL FACTS: THE NEXT FRONTIER? (2008), *available at* http://www.isscr.org/public/ISSCR08_PubEdBroch.pdf; and International Society for Stem Cell Research, FAQ, http://www.isscr.org/public/faq.htm (last visited Apr. 30, 2009).

for example, were first developed in animal models. Research using animal stem cells of different types is not controversial and has been routinely supported by the NIH.

Research using human stem cells is more politically complex. So-called "adult" stem cells,[2] which are typically irreversibly developed and more specialized in that they can generally only be converted into a limited range of more specialized cells, were initially isolated in the 1950s. These cells have come to be used as part of treatment regimes for some diseases, particularly those that require the replacement of the immune system. Hematopoietic stem cells, for example, which can be isolated from bone marrow, are regularly used to replenish the blood cells that are destroyed by treatments for leukemia and other forms of cancer. Research using these types of stem cells, which occur naturally in the body and can be isolated without any adverse effects, is not particularly controversial and is regularly funded by NIH and other organizations that support biomedical research.

By contrast, research using human embryonic stem cells has been extremely controversial. These cells, which were isolated in the late 1990s, form during the development of a fertilized human embryo and are extracted in the first few days of the embryo's growth. These cells are, at least in theory, capable of being turned into all of the body's specialized cell types and thus are potentially usable to treat a broader range of diseases than more specialized (less flexible) adult stem cells. The controversy surrounding research using these cells arises from the fact that the extraction of the stem cells destroys the embryo, which many critics find ethically unacceptable.[3]

Several recent scientific developments may allow the creation of stem cell lines without the destruction of embryos.[4] Most visibly, several groups have developed "induced pluripotent stem cells" (iPSCs) by using genetic manipulation to turn a skin cell into cells that closely resemble embryonic stem cells.[5] This ability to reverse the development of an existing cell and turn it into a

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2. The term "adult" is confusing, since these cells do not necessarily come from chronological adults. Some varieties of "adult" stem cells, in fact, can be isolated from the blood in the umbilical cords of new born infants or the pulp under baby teeth. The use of the term "adult" comes from the fact that these stem cells are found in tissue that has already developed.

3. *But see* PRESIDENT'S COUNCIL ON BIOETHICS, ALTERNATIVE SOURCES OF HUMAN PLURIPOTENT STEM CELLS 24 (2005), *available at* http://www.bioethics.gov/reports/white_paper/alternative_sources_white_paper.pdf (discussing techniques for removing cells from "live" embryos in a process similar to pre-implantation genetic diagnosis).

4. *See* Rajesh Rao, *Alternatives to Embryonic Stem Cells and Cloning: A Brief Scientific Overview*, 9 YALE J. HEALTH POL'Y L. & ETHICS 603 (2009).

5. M. William Lensch, *Breakthroughs in Stem Cell Biology: Human iPS Cells*, STEM CELL BRIEFINGS (Int'l Soc'y for Stem Cell Research, Deerfield, Ill.), Feb. 27, 2008, http://www.isscr.org/public/briefings/breakthrough.html. For a more detailed explanation, see

stem cell, which may then be turned into an entirely different type of cell, has become politically controversial. Detractors of hESC research have argued that the availability of this and other alternative techniques to produce stem cell lines lessens or eliminates the need to support research using hESCs. Many scientists argue such a conclusion is premature, noting that iPSCs have not been demonstrated to be acceptable substitutes for hESCs, which will remain the "gold standard" for stem cell research for some time to come.[6]

II. FEDERAL REGULATION AND FUNDING

In spite of considerable public attention to stem cell-related issues over the last fifteen years, there is little consensus about the appropriate scope and financing for hESC research.[7] Debate in Washington has generally not addressed the permissibility or legality of embryonic stem cell research, but it has rather focused on the narrower question of which stem cell "lines" should be eligible to receive federal financial support through the NIH and other federal agencies.[8] The Bush administration, together with some (though not all) religious and pro-life groups, argued consistently that human embryos have the same moral status as human life and that research destroying embryos should be restricted, if not entirely prohibited. Many Democrats, together with disease advocacy groups and some pro-life Republicans, have disputed this characterization of the moral status of the embryo and have argued that hESC research presents considerable potential for treating a wide range of diseases.

The use of federal funds to create, destroy, or harm embryos for research purposes has been routinely prohibited in appropriations bills since the mid-1990s through the so-called Dickey-Wicker Amendment.[9] Subsequent debate, however, has relied on arguments that this prohibition does not extend to

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Gretchen Vogel, *Breakthrough of the Year: Reprogramming Cells*, 322 SCIENCE 1766 (2008).

6. For a recent example of these competing positions, see Rob Stein, *Researchers Find Safer Way To Produce Stem Cell Alternative,* WASH. POST, Mar. 2, 2009, at A5.

7. For a history of federal policy in this area, see PRESIDENT'S COUNCIL ON BIOETHICS, MONITORING STEM CELL RESEARCH 21-52 (2004), *available at* http://www.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf.

8. *See e.g.*, Ceci Connolly, *2 GOP Senators Defend Bush on Stem Cell Research*, WASH. POST, Aug. 13, 2004, at A2; Rick Weiss, *Approved Stem Cells' Potential Questioned*, WASH. POST, Oct. 29, 2004, at A3; Rick Weiss, *Bill Renews Fight on Stem Cells*, WASH. POST, Feb. 17, 2005, at A6.

9. The original amendment can be found in the Balanced Budget Downpayment Act, Pub. L. No. 104-99 § 128, 110 Stat. 26, 34 (1996) (affecting NIH funding for FY 1996 contained in Pub. L. No. 104-91, 110 Stat. 7 (1996)). For subsequent fiscal years, the rider is found in Title V, General Provisions, of the Labor, HHS and Education appropriations acts. *See* JUDITH A. JOHNSON & ERIN D. WILLIAMS, CONGRESSIONAL RESEARCH SERV., CRS REPORT FOR CONGRESS: STEM CELL RESEARCH 2 n.7 (2005), *available at* http://fpc.state.gov/documents/organization/51131.pdf.

research on stem cell lines created using other funding sources.[10] The Clinton administration advocated an expansive view of this argument, which would have encouraged researchers to fund the creation of stem cell lines from other sources and then apply for federal funds to continue research on these "pre-existing" lines.[11] The Bush administration, by contrast, largely limited federal funding support to the small number of lines existing before 2001. The more recent development of techniques for devising stem cell lines that do not require the destruction of embryos led to an executive order signed in 2007, which expanded eligibility to stem cell lines developed "without creating a human embryo for research purposes or destroying, discarding or submitting to harm a human embryo or fetus."[12] The NIH developed elaborate guidance for defining "harm" to an embryo or fetus, but this executive order was revoked by President Obama's recent order.[13]

The Bush administration also adopted an unusually restrictive policy that prohibited the direct or indirect use of federal funds to support research on ineligible stem cell lines.[14] In order to avoid jeopardizing their federal funds, many universities and other research institutes found it prudent to build separate labs and purchase completely separate equipment to be used in hESC research. These facilities still draw on non-federal sources of funding, allowing research institutes to avoid charges that they are using, for example, lab equipment originally purchased with federal funds to indirectly support research on ineligible stem cell lines.[15]

Despite considerable effort, the federal policymaking process has not been successful in moving hESC research policy in any particular substantive direction. By one count, more than forty separate pieces of legislation have been introduced since 2001 in this general area, ranging from attempts to prohibit or

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10. *See* JOHNSON & WILLIAMS, *supra* note 9; George Q. Daley, *Missed Opportunities in Embryonic Stem-Cell Research*, 351 NEW ENG. J. MED. 627 (2004).

11. *See* National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells, 65 Fed. Reg. 51,976 (Aug. 25, 2000) (guidelines under the Clinton administration).

12. Exec. Order No. 13,435, 72 Fed. Reg. 34,591 (June 20, 2007).

13. For details, see NAT'L INSTS. OF HEALTH, PLAN FOR IMPLEMENTATION OF EXECUTIVE ORDER 13435: EXPANDING APPROVED STEM CELL LINES IN ETHICALLY RESPONSIBLE WAYS (2007), *available at* http://stemcells.nih.gov/staticresources/policy/eo13435.pdf. For an explanation of the political context surrounding this executive order, see Rick Weiss, *Future of Stem Cell Tests May Hang on Defining Embryo Harm*, WASH. POST, July 29, 2007, at A8. For the revocation of this order, see Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

14. Roger G. Noll, *The Politics and Economics of Implementing State-Sponsored Embryonic Stem-Cell Research* 20-21 (Stanford Inst. for Econ. Policy Research, Discussion Paper 04-28, 2005), *available at* http://www.stanford.edu/group/siepr/cgi-bin/siepr/?q=system/files/shared/pubs/papers/pdf/04-28.pdf.

15. *See, e.g.*, Claudia Driefus, *At Harvard's Stem Cell Center, the Barriers Run Deep and Wide*, N.Y. TIMES, Jan. 24, 2006, at F2.

even criminalize all cloning research to efforts to expand the scope and scale of federal support for hESC research.[16] None of these initiatives has become law. Congress twice passed, and President Bush twice vetoed, legislation that would have expanded federal support to cell lines derived from embryos created, but not used, for *in vitro* fertilization.[17] There are large numbers of these unused embryos, most of which will likely be destroyed, currently being stored at fertility clinics. The bills Congress passed would have allowed researchers to use federal funds to develop stem cell lines from these embryos if the individuals who deposited them donated them for research. The Dickey-Wicker Amendment continues to limit federal funding for research that would entail the destruction of embryos;[18] however, current federal law imposes no restrictions on research funded by private or other non-federal funds.

As a result of these funding limits, federal support for hESC research has historically been small. Appendix A displays past and estimated funding levels by the NIH for hESC research and other kinds of stem cell research for the last six fiscal years. Total NIH funding for all kinds of stem cell research has increased over this period by approximately twenty percent, from $553 million to $938 million annually. Spending on hESC research, however, amounts to only about nine percent of this total, or slightly less than $90 million annually. Other forms of stem cell research that are not particularly controversial attract more support and account for the bulk of growth in spending over this period. There are no limits on other stem cell research activities of the sort that have been attached to hESC research. Researchers have developed treatments using other types of human stem cells, and many of the techniques used to isolate or manipulate embryonic stem cells have been developed using animal cells. Direct federal support to date for hESC research has been limited. As Appendix A notes, spending for all forms of stem cell research is relatively small compared to NIH support in such areas as cancer, genetics, biotechnology, and cardiovascular research, and support for hESC research is roughly comparable to NIH spending on Alzheimer's disease, diagnostic radiology, and eye diseases.

III. STATE ACTIONS AND FUNDING

While decisive federal action around hESC research has proven impossible to date, more than a few states have been able to establish coherent state research policies. As in numerous other areas, advocates frustrated by the deadlock in

16. FRANCIS FUKUYAMA & FRANCO FURGER, BEYOND BIOETHICS: A PROPOSAL FOR MODERNIZING THE REGULATION OF HUMAN BIOTECHNOLOGIES 129 (2007).

17. *See* Stem Cell Research Enhancement Act of 2005, H.R. 810, 109th Cong. (2006); Stem Cell Research Enhancement Act of 2007, S. 5, 110th Cong. (2007).

18. Sheryl Gay Stolberg, *New Stem Cell Policy To Leave Thorniest Issue to Congress*, N.Y. TIMES, Mar. 9, 2009, at A1.

Washington have been able to move their agendas forward at the state level. While policymakers in many states have avoided becoming involved in the complex and controversial issues surrounding hESC research, others have been able to construct majorities around particular approaches to this research. Like the legislation proposed but not enacted at the federal level, the legislation actually enacted by states has been extremely diverse in scope and intent. These state laws range again from legislation to prohibit and even criminalize hESC research to active encouragement of hESC research inside state borders and authorization of considerable amounts of state funds to support it.[19] At the time of this writing, five states ban or restrict hESC research,[20] while as many as ten have supported it in some form.[21]

State financial support for stem cell research is particularly significant because few states have any experience with supporting biomedical research on a large scale. While some states have supported various kinds of targeted research initiatives at state universities to encourage other types of technology, almost no states have experience with operating competitive, peer-reviewed research programs in medicine or genetic research. Funding from the NIH and other federal agencies has been ubiquitous in biomedical research, so states have not previously felt compelled to support research in these areas.

In spite of this limited experience, several states have approved, and more have proposed, substantial spending from state sources to support stem cell research. A summary of state activity to date is presented in Appendix B. There is no authoritative source of comparable data on state spending on stem cell research, and it is frequently difficult to use publicly available information to

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19. For an excellent recent review of state activities, see generally Aaron D. Levine, *Policy Considerations for States Supporting Stem Cell Research: Evidence from a Survey of Stem Cell Scientists*, 68 PUB. ADMIN. REV. 681 (2008). Current and pending state legislation on these issues can be tracked at National Conference of State Legislatures, Stem Cell Research, http://www.ncsl.org/programs/health/genetics/embfet.htm (last visited Apr. 30, 2009).

20. These states are Arkansas, Indiana, Louisiana, North Dakota and South Dakota. *See* Dahleen Glanton, *A Stem Cell Battle Along State Lines*, L.A. TIMES, Mar. 13, 2009, at A21, *available at* http://www.latimes.com/news/nationworld/nation/la-na-stemcells-states13-2009mar 13,0,773884.story; *see also* National Conference of State Legislatures, *supra* note 19 (listing states' restrictions on research with embryos and fetuses). Other states have begun considering enacting legislation in the wake of Executive Order 13,505. *See* Shaila Dewan, *After Change in Federal Policy, Some States Take Steps To Limit Stem Cell Research*, N.Y. TIMES, Mar. 13, 2009, at A9, *available at* http://www.nytimes.com/2009/03/14/us/politics/14stem.html.

21. These states are California, Connecticut, Illinois, Maryland, Massachusetts, Minnesota, New Jersey, New York, Ohio, and Wisconsin, as I will discuss here. For a continually updated listing of state activities related to stem cell research, see National Conference of State Legislatures, *supra* note 19 (noting additional support for adult stem cell but not embryonic stem cell research in Indiana and Virginia and activities by Washington that may enable future funding of stem cell research).

apportion various forms of state spending between hESC research and other forms of stem cell research.

By far the largest state initiative to date has been in California. In 2004, California voters approved an initiative to spend $3 billion, financed by state general obligation bonds, over a period of ten years to support stem cell research. The California Institute for Regenerative Medicine (CIRM), the agency that manages the state's stem cell program, has already allocated over $600 million in hESC research support, or more than five times what NIH is allocating annually to these activities.[22]

Other state allocations to date have been smaller. Ohio and Minnesota have made "one time" appropriations for adult stem cell research and capital construction, respectively. New Jersey, Illinois, and Connecticut have allocated research grants of varying sizes, and New Jersey has also approved funds for the construction of a stem cell laboratory, although a bond issue to support an ongoing research program was defeated in 2007.[23] Connecticut has approved ongoing support for stem cell research programs from tobacco settlement revenues,[24] and Maryland has made multiple awards supported by general state revenues.[25] Wisconsin has not made separate appropriations of state funds to support hESC research, but the state has been aggressively promoting stem cells as an economic development strategy.[26] University of Wisconsin is a major center for hESC research—the university is one of the places where hESCs were first isolated in the late 1990s—and the state holds important patents in hESC technology. The university also houses the National Stem Cell Bank, established

22. *See* California Institute for Regenerative Medicine, Welcome, http://www.cirm.ca.gov (last visited Apr. 30, 2009) (detailing the California funding allocation and CIRM approval of more than $693 million in grants to date).

23. For a description of the bond issue's defeat, see Richard G. Jones & Kareem Fahim, *Bid for Stem Cell Financing Was Late and Lukewarm, Organizers Concede*, N.Y. TIMES, Nov. 9, 2007, at B1, *available at* http://www.nytimes.com/2007/11/09/nyregion/09abort.html.

24. The enabling legislation (Connecticut Public Act 05-149; Senate Bill 934) appropriated $20 million from state general funds to support the first two years of research grants and also authorized the transfer of $10 million annually from the state Tobacco Settlement Fund to the state's Stem Cell Research Fund for the next eight years (fiscal years 2008 to 2015). *See* 2005 Conn. Legis. Serv. No. 05-149 (West) (codified as amended at CONN. GEN. STAT. ANN. §§ 19a-32d to -32g (West 2006)); Connecticut Department of Public Health, Stem Cell Research Program – About CT's Program, http://www.ct.gov/dph/cwp/view.asp?a=3142&Q=389690 (last visited Apr. 30, 2009).

25. For details on funding and financial resources for the Maryland program, see Maryland Stem Cell Research Fund, About Us, http://www.mscrf.org/content/aboutus/index.cfm (last visited Apr. 30, 2009).

26. For a brief description of these efforts, see Press Release, Office of the Governor, Governor Doyle Announces $1 Million for Stem Cell Start-Up Company (Oct. 10, 2006), *available at* http://www.wisgov.state.wi.us/journal_media_detail.asp?prid=2362.

by NIH to maintain and distribute many of the stem cell lines that could be researched using federal funds.[27]

Larger state stem cell programs are in the works. The FY 2008 New York State budget appropriated $100 million in state funding to establish a stem cell research program, and there are plans for additional funding, although the potential source remains unclear.[28] The state has made two rounds of awards, has issued a strategic plan, and is soliciting applications for other funding. Massachusetts recently passed a $1 billion life sciences initiative that includes an indeterminate amount for stem cell research.[29] Both states are major centers for hESC research, and there appears to be significant bipartisan political support for ongoing state funding. Both states have also taken care to spread initial spending broadly in terms of geography, thereby maximizing the number of areas and legislative districts with an economic stake in continued funding.

At least some of these state initiatives appear to be sustainable into the Obama administration. California's Proposition 71 authorized the disbursement of $3 billion in research funds over ten years, and CIRM management has begun to lobby for additional funding sources past this time horizon.[30] Connecticut has earmarked $100 million in state funds over a decade. Existing programs in New York and Massachusetts also contemplate ongoing funding for stem cell research. Although the New Jersey bond issue to support stem cell research was defeated, the state's governor has discussed plans to support this research by other means, and the state has made small economic development grants to biotech firms interested in stem cell therapies.[31] Maryland, by contrast, relies on annual state appropriations to support stem cell research. While annual appropriations are less reliable than earmarked bond proceeds, strong political support may produce stable funding. Recent budget problems may have reduced the size of programs in some states, but there is no evidence as yet that states are abolishing stem cell programs in response to financial difficulties. There have

27. President Obama's executive order has now removed many line-based restrictions on federal funding for hESC research. Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

28. *See* EMPIRE STATE STEM CELL BD., STRATEGIC PLAN 14 (2008), *available at* http://stemcell.ny.gov/docs/NYSTEM_Strategic_Plan_FINAL.pdf.

29. For a description of the Massachusetts initiative, see the website of the Massachusetts Life Sciences Center, the state agency which directs the program. The Massachusetts Life Sciences Center, http://www.masslifesciences.com/mission.html (last visited Apr. 30, 2009).

30. These efforts include pursuing funding from the Obama administration's economic stimulus plan and private placement of state bonds. For details, see the ongoing coverage in the California Stem Cell Report blog. California Stem Cell Report, http://californiastemcell report.blogspot.com (last visited Apr. 30, 2009).

31. Alex Philippidis, *Corzine To 'Revisit' Stem-Cell Referendum as Calif. Company Expands to New Jersey*, BIOREGION NEWS, May 5, 2008, http://www.genomeweb.com/bioregionnews/corzine-%E2%80%98revisit%E2%80%99-stem-cell-referendum-calif-company-expands-new-jersey (free subscription required for access).

been public complaints about the failure of state programs to yield tangible results and a variety of issues raised about program management, particularly in California, but there have been no serious political challenges as yet to these programs' continued existence.[32]

Several states have begun to shift the form of support they offer away from research-oriented grants to universities and towards support of for-profit companies aimed at product development. California has recently awarded its first substantial grants to private companies[33] and is in the process of developing a loan program targeted at biotechnology companies involved in the development of stem cell therapies.[34] The Massachusetts Life Science Center, whose mandate includes support for stem cell research, has funded no stem cell activities to date beyond a registry of stem cell lines and a stem cell "bank." The Center's only "round" of funding to date, which did not involve any stem cell projects, supported joint projects by universities and private companies. This pattern suggests that further state support for stem cell research, when it comes, may be more "applied" or "translational" in nature rather than aimed at university-based research.[35]

In addition to providing significant financial support for stem cell research not eligible for federal funding, these state initiatives also have established centers of policymaking for stem cell research independent of federal influence. States that have established funding programs for stem cell research have been compelled to develop regulations governing the types of research that will be supported, acceptable sources and payment for stem cell lines to be used in funded research, intellectual property, an acceptable "return" to state governments on their research investment, and a variety of other complex issues. While most states appear to have relied heavily for many of these issues on model guidelines promulgated by the National Academy of Sciences and the International Society for Stem Cell Research,[36] state policies differ substantially.

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32. *See, e.g.*, Thomas Lee, *Stem Cells: Time to Make Good on Promises*, MINNEAPOLIS STAR TRIB., Sept. 28, 2008, at 1D, *available at* http://www.startribune.com/business/29828789.html; Bernadette Tansey, *Obama Policy a Lift for Stem Cell Researchers*, S.F. CHRON., Nov. 29, 2008, at A1, *available at* http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2008/11/29/MN76147PBR.DTL.

33. *Business Snags $5.3 Million from CIRM*, California Stem Cell Report, Dec. 15, 2008, http://californiastemcellreport.blogspot.com/2008/12/business-snags-53-million-from-cirm.html.

34. *$500 Million CIRM Lending Program Up on Wednesday; Details Missing*, California Stem Cell Report, Jan. 18, 2009, http://californiastemcellreport.blogspot.com/2009/01/500-million-cirm-lending-program-up-on.html.

35. *See* Ben Butkus, *Massachusetts LSC Awards $3.7M to Spur Public-Private R&D Partnerships*, BIOTECH TRANSFER WEEK, Dec. 31, 2008, http://www.genomeweb.com/biotechtransferweek/massachusetts-lsc-awards-37m-spur-public-private-rd-partnerships.

36. The National Academy guidelines are contained in COMM. ON GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH, GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH (2005), *available at* http://www.nap.edu/openbook.php?isbn=0309096537, with amendments

Some states restrict eligibility for funding to universities and other nonprofit research institutes, for example, while others contemplate grants to for-profit companies or consortia of companies and universities. Some state regulations prohibit the use of state funds to pay donors of eggs that will be used in developing stem cell lines; others require only assurances that the donation of eggs has been voluntary. While the potential for conflict between the policies of different states may complicate attempts for researchers to collaborate across state lines, several states have established a consortium (the Interstate Alliance on Stem Cell Research) to identify and ameliorate such conflicts.[37] The existence of state laws and regulations (or, in the case of California, covenants with bondholders) governing the expenditure of state funds for stem cell research may complicate any federal efforts to expand regulation of this research beyond those projects supported with federal funds.

A second reason for expecting state stem cell programs to persist is that they appear to have been effective tools for state economic development. Levine's recent work suggests that state funding and permissive state policies that place few limits on stem cell research have been effective in creating awareness among stem cell scientists of differences among states, causing permissive states to be seen as more attractive research environments.[38] Some states have been aggressively recruiting scientists from other states, which may continue to generate demands for support from medical schools and other institutions fearful of losing productive researchers.

IV. PRIVATE PHILANTHROPY AND STEM CELL RESEARCH

A second major source of funding for hESC research and other forms of stem cell research has been private philanthropy. While private support, even on a large scale, to support biomedical research is nothing new, private support for stem cell research in general, and hESC research in particular, has been unusual in two ways: it is large relative to the scale of the research enterprise and the level of federal support, and it has been used for a broader array of activities than has been typical.

While a comprehensive accounting of private contributions to stem cell research is impossible, a listing of some recent large, visible gifts is provided in Appendix C. This list is incomplete. Many national foundations which finance

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issued in 2007 and 2008. The International Society for Stem Cell Research guidelines are contained in INT'L SOC'Y FOR STEM CELL RESEARCH, GUIDELINES FOR THE CONDUCT OF HUMAN EMBRYONIC STEM CELL RESEARCH (2006), *available at* http://www.isscr.org/guidelines/ISSCRhESC guidelines2006.pdf.

37. For details, see the Alliance's website at Interstate Alliance on Stem Cell Research, Welcome, http://www.iascr.org/ (last visited Apr. 30, 2009).

38. Levine, *supra* note 19.

research into particular diseases, such as the Juvenile Diabetes Research Foundation, the Michael J. Fox Foundation for Parkinson's Research, and the Leukemia and Lymphoma Society, fund stem cell research projects; other foundations and donors may also fund stem cell projects at individual institutions. The overall size of these donations is difficult to identify, although a *Wall Street Journal* article has claimed that private funding constitutes the primary source of support for hESC research.[39] This list also excludes investment by private companies and venture capital funds for stem cell-related projects. One published estimate places venture capital investment in stem cell companies of all types at $1.1 billion between 1995 and 2007, a modest amount by venture capital standards.[40] This investment is almost certainly focused on products developed from adult stem cells, which have not been as controversial as embryonic stem cells. More recent anecdotal reports suggest that venture capital investment in adult stem cell companies may have accelerated as more products are developed, although many of these products are at the pre-clinical trial stage.[41]

While this list is incomplete, it reports gifts totaling some $2.7 billion, a large amount given the current scale of federal funding and the overall size of the stem cell research enterprise. Itemizing the activities that these funds are intended to support, separating support for hESC research from other stem cell research funding, or identifying the time period over which these funds are to be spent is impossible with any degree of precision. It seems reasonable, however, to infer that much of this funding, particularly to institutions in California, Massachusetts, New York, and Maryland that are already major centers of hESC research, goes to support hESC research in various ways. Contributions to establish stem cell research centers at particular universities are common, which may mean that these funds support the acquisition of lab space and equipment, salaries for key center personnel, and other "overhead" or "start-up" functions as well as activities more directly related to biomedical research. The Harvard Stem Cell Institute, for example, has developed several hESC "lines" that are available to other researchers in addition to supporting its own research program.[42] The

39. Robert J. Hughes, *Stem Cell Funding's Private Side*, WALL ST. J., July 28, 2006, at W2.

40. Lee, *supra* note 32 (citing an estimate by MoneyTree, Inc.).

41. *See, e.g.*, Chuck Soder, *Stem Cell Progress Aiding Firms' Product Commercialization Plans*, CRAINS CLEVELAND BUS., Jan. 5, 2009, at 1; John Sterling, *Toucan Capital Holds Largest Portfolio of Stem Cell and Regenerative Medicine Companies*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Jan. 23, 2009, http://www.genengnews.com/news/bnitem.aspx?name =48528449. For examples of products that have been through initial clinical trials, see Amy Coombs, *Stem Cells for the Heart, a New Wave of Clinical Trials*, NATURE REP. STEM CELLS, Apr. 10, 2008, http://www.nature.com/stemcells/2008/0804/080410/full/stemcells.2008.55.html.

42. *See Approval Granted for Harvard Stem Cell Institute Researchers To Attempt Creation of Disease-Specific Embryonic Stem Cell Lines*, HARV. U. GAZETTE, June 6, 2006,

largest gifts in this Appendix, however, are donations of stock to the Stowers Research Institute in Missouri that cannot be allocated easily to any particular activity.[43]

One novel trend, at least in California, is the use of private money to directly support the activities of government agencies. CIRM management actively solicited donations amounting to some $18 million from private parties to pay the organization's initial operating expenses, and the agency will occupy office space in downtown San Francisco rent- and utility-free for a decade as a result of private contributions.[44] Private donors also supported CIRM's research program through the purchase of low interest Bond Anticipation Notes,[45] which were repaid once the bond issue authorized by Proposition 71 was sold. A similar use of private placements has been suggested as a possible means of coping with the state of California's suspension of bond issues to address extremely severe budget problems.[46] The Massachusetts proposal for state support of stem cell research also includes $250 million in private matching funds to be used in conjunction with state funding.[47]

The sustainability of private donations at this level to support stem cell research in general and hESC research in particular is unclear. Many disease foundations support stem cell research, including hESC research, as part of their

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http://www.hno.harvard.edu/gazette/daily/2006/06/06-stemcell.html.

43. The Stowers situation is complicated. As described in Institute publications, "far more" of the Institute's research program to date has involved adult and germ-line stem cells than embryonic stem cells. Institute management has attempted to expand its embryonic stem cell research program, but persistent attempts by the Missouri legislature to restrict or criminalize this research has made it difficult to attract researchers to the Institute's Kansas City campus. In response to the ongoing political debate in Missouri, the Institute has funded embryonic stem cell research underway at Harvard, which is listed in Appendix B, moved significant endowment assets from Missouri to a Delaware-based non-profit organization, and has recently announced it is putting further expansion plans in Missouri on hold until the political environment stabilizes. *See* William B. Neaves, *Why the Stowers Institute Supports Stem Cell Research*, STOWERS REP., Fall 2006, at 2, 2; Stephanie Simon, *Stem Cell Dissent Roils States*, L.A. TIMES, Aug. 1, 2007, at A12; Rob Roberts, *Stowers Puts Expansion Plans on Hold*, KANSAS CITY BUS. J., Jun. 28, 2007, http://kansascity.bizjournals.com/kansascity/stories/2007/06/25/daily37.html.

44. David Hamilton, *Donors Sustain Stem Cell Effort in California Amid Funding Battle*, WALL ST. J., Aug. 16, 2006, at A1.

45. *See* Karen Gullo & Rob Waters, *California's $3 Bln Stem Cell Bonds Approved by Judge*, BLOOMBERG.COM, Apr. 21, 2006, http://www.bloomberg.com/apps/news?pid=10000103&sid=aF7GZ7xaVaoY&refer=us.

46. For details, see Ron Leuty, *State's Budget Crisis Could Strain Stem Cell Research Efforts*, SILICON VALLEY/SAN JOSE BUS. J., Dec. 19, 2008, http://sanjose.bizjournals.com/sanjose/stories/2008/12/22/story7.html?jst=pn_pn_lk.

47. Commonwealth of Massachusetts, Massachusetts Life Sciences Initiative Strategy, http://www.mass.gov/Agov3/docs/mass_life_sciences_strategy.rtf (last visited Apr. 30, 2009).

ongoing research funding activities, and total hESC research funding from this source may well exceed funding by the federal government. While disease foundations typically do not report funding amounts for stem cell or any other particular line of research in their annual reports or financial statements, the Juvenile Diabetes Research Foundation, one of the larger disease foundations, by itself spent approximately $4.9 million in FY 2008 on hESC research.[48] Even if support from other individual disease foundations is smaller, it would not be difficult for total foundation support to exceed federal funding. As noted in Appendix C, several universities have also established large fundraising campaigns to support hESC and other stem cell research, which may be successful to some degree in establishing a stable flow of funds for individual campuses. In addition, the recent decline in the stock market may have significantly reduced the net worth of many foundations and lessened their ability to continue to support research at this level. While there may be fewer large grants to establish new research programs or build labs independent of the current NIH funding restrictions, there may be enough ongoing support for foundations and other private donors to continue to outspend NIH on hESC research.

While a conclusive accounting appears impossible, the available evidence strongly suggests that both state governments and private foundations are outspending the federal government in the support of hESC research and have become major policymakers around stem cell research. California has been particularly active in this regard: the state is currently the largest supporter of hESC research in the world and has been actively seeking collaborative relationships with funding agencies in other countries. Because the federal government has limited its support of stem cell research, it has exercised significantly less influence in stem cell research policy than in other scientific areas. Some observers have suggested that this regulatory picture may change with the Obama administration and a new Congress. I now turn to an examination of the likely future of hESC research policy and funding.

V. OBAMA'S EXECUTIVE ORDER AND THE OUTLOOK FOR STEM CELL FUNDING

Some observers expected this picture to change dramatically with a new administration and a new Congress.[49] The picture has clearly changed, but it is

48. Juvenile Diabetes Research Foundation, Stem Cell Facts, http://advocacy.jdrf.org/files/General_Files/Advocacy/2009/Stem_Cell_Therapies.pdf (last visited Apr. 30, 2009); *see also* Hughes, *supra* note 39.

49. *See, e.g.*, Carl Hulse, *Democrats Weigh Methods To End Stem Cell Ban*, N.Y. TIMES, Jan. 3, 2009, at A11; Gautam Naik & Robert Lee Hotz, *Obama's Promise on Stem Cells Doesn't Ensure New War on Disease*, WALL ST. J., Nov. 25, 2008, at A9, *available at* http://online.wsj.com/article/SB122757360662054989.html.

still uncertain how dramatic the change will prove to be. After some pressure from advocates, President Obama recently signed an executive order that repealed the Bush administration's restrictions on the stem cell lines that federal funding can be used to support, eliminated the requirement that federally supported research be segregated from that on ineligible lines, and revoked Bush's recent executive order allowing federal support for research only on lines created by means that did not destroy or harm an embryo.[50] The order was, however, narrowly drawn and articulated no particular standards to govern the origins of lines that would qualify for federal funds. The only standard referenced in the order is "to the extent permitted by law." To fill this gap, the NIH were directed to issue "guidance on such research" within 120 days.[51] The President has not called for the abolition of the Dickey-Wicker amendment, and his chief domestic policy advisor has been quoted to the effect that the administration will have no position on the issue.[52] In similar fashion, the administration has not called explicitly for an expansion of funding for embryonic stem cell research and has not endorsed more controversial means of producing embryonic stem cells such as somatic cell nuclear transfer.[53]

This failure on the part of the President to endorse any particular standard for stem cell lines, the transfer of responsibility for promulgating standards to NIH (thus effectively delaying a decision on the administration's stem cell policy), and the staging of the event at which the order was signed provide circumstantial evidence for the prediction that the administration is unlikely to seek more than incremental change in stem cell policy in the short run. The event was announced at a time when it was unlikely to attract major media attention, and the signing of the executive order was coupled with the signing of a presidential memorandum on scientific integrity rather than being the sole subject of the presidential appearance. The President's statement at the signing took some care to acknowledge opposing views on stem cell research and promised "strict guidelines, which we will rigorously enforce" in the conduct of stem cell research.[54]

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50. Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

51. For an explanation, see Rob Stein, *Obama's Order on Stem Cells Leaves Key Questions to NIH*, WASH. POST, Mar. 10, 2009, at A1, *available at* http://www.washingtonpost.com/wp-dyn/content/article/2009/03/09/AR2009030903156.html.

52. *See* Stolberg, *supra* note 18.

53. Somatic cell nuclear transfer is a technique in which the nucleus of a fertilized egg is replaced with the nucleus of a somatic cell from a potential patient and then allowed to develop to the point where stem cells can be collected. It has the potential virtue of producing cells and tissues that are compatible with the patient's body and will not be attacked by the patient's immune system. For details, see Richard Mollard, *Somatic Cell Nuclear Transfer (SCNT) or Therapeutic Cloning*, International Society for Stem Cell Research, http://www.isscr.org/public/therapeutic_cloning.pdf (last visited Apr. 30, 2009).

54. *Transcript: Obama's Remarks on Stem Cell Research*, N.Y. TIMES, Mar. 9, 2009,

These circumstances suggest that the administration policy and the NIH guidelines, when they appear, are likely to focus on incremental modifications to existing policy. Perhaps the most obvious candidate for such changes would involve standards proposed in bills which Congress has already passed twice which expand the number of stem cell lines eligible for federal financial support.[55] These standards would expand eligible lines to include cells derived from embryos initially created but no longer needed for reproductive purposes, which would otherwise have been destroyed; these embryos will need to have been donated under appropriate standards for informed consent.

While the elimination of the Bush administration's restrictions and expansion of eligible lines along the lines Congress has already approved are not trivial, these changes will not directly expand federal support for stem cell research of any sort or significantly expand the heretofore limited federal role in the governance of this research. It is uncertain, however, whether the administration and its congressional allies will seek more than incremental changes in stem cell funding or substantial legislative changes that would significantly alter the existing decentralized stem cell governance structure. It might be argued that there are substantial reasons for the Obama administration, and for stem cell allies more generally, not to push for more serious changes in federal stem cell policy in the short run.

Perhaps the most obvious reason for *not* pursuing more dramatic change in stem cell policy is the demand for political capital and attention from other equally or more pressing problems. The Obama administration and new Congress have inherited wars in Iraq and Afghanistan, flare-ups in the Middle East, extremely expensive and divisive ongoing repairs to the country's financial system and overall economy, controversial anti-terrorism policies, and increasing problems with health care coverage and global warming, among other difficulties. Dealing with these issues, which are more or less mandatory items on the national agenda, is likely to prove protracted and controversial, making it possible that a new Congress and President simply will not have the time or energy to address the complex, controversial, but non-crisis issues associated with significantly altering the federal role in stem cell research. An executive order or legislation of the scope described above would address issues that have already been discussed and debated at some length before being passed twice by

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http://www.nytimes.com/2009/03/09/us/politics/09text-obama.html (not published in the print edition).

55. *See supra* note 17. As this Article was going to press, NIH issued draft guidelines expanding the number of stem cell lines eligible for federal funding along the lines suggested here. After a period of public comment, final guidelines will be issued in the summer of 2009. Draft National Institute of Health Guidelines for Human Stem Cell Research Notice, 74 Fed. Reg. 18,578 (proposed Apr. 23, 2009). For an explanation of the political context, see Ceci Connolly, *Compromise Rules Issued on Embryonic Stem Cells*, WASH. POST, Apr. 18, 2009, at A4.

Congress. While likely to attract strenuous protest from stem cell detractors, this particular set of changes already has a pre-existing majority that has determined that supporting it is in its political interest. Other changes have not received this level of prior attention from the political process and may well be more controversial and harder to resolve, raising the real possibility that a stem cell reform bill could become gridlocked in Congress.

Several other factors contribute to the likelihood of congressional gridlock around stem cell research. One is that a number of important issues around this research remain politically controversial, and a congressional majority in favor of reform cannot be assumed. The last two congressional elections have produced significant Democratic majorities in both the House and the Senate, but many Democratic gains have been in districts and states traditionally held by Republicans, which means that the Democrats newly occupying these seats may have to worry about electorates who are more dubious about the benefits of stem cell research than those from traditionally Democratic areas. The Dickey-Wicker amendment has been attached to every Department of Health and Human Services appropriations bill since 1996,[56] but there has been little serious discussion of this restriction and no serious attempt to abolish it. There is no ready-made majority for eliminating this restriction, as there may be for expanding the number of stem cell lines eligible for federal funding.

Beyond debate over funding research involving the destruction of embryos, controversy exists over the question of payment for eggs. Infertile couples are currently allowed to offer payment for others' eggs for use in reproductive therapies, but payment for eggs for *research* purposes is currently illegal in most states (although payment for expenses and lost wages is sometimes permissible).[57] Researchers and advocates have increasingly complained that the lack of embryos from which to extract stem cells constitutes a major barrier to research progress and that efforts to solicit donations of eggs have largely proved unsuccessful. Legislative efforts to allow the use of federal funds to pay egg donors, however, are likely to prove quite controversial with at least some groups. Interested parties particularly include women's health advocacy groups that support stem cell research, but express strong concern about the risks associated with egg extraction procedures and the vulnerability of lower-income women to offers of significant amounts of cash.[58]

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56. See JOHNSON & WILLIAMS, *supra* note 9, at 2 n.7.

57. For further details and a listing of state restrictions on the purchase or sale of human tissue, see National Conference of State Legislatures, *supra* note 19.

58. *See, e.g.*, *The Implementation of Proposition 71, the Stem Cell Research and Cures Act: Joint Informational Hearing of the S. Subcomm. on Health, S. Subcomm. on Stem Cell Research Oversight, and the Assembly Comm. on Health*, 2005 Leg., 2005-2006 Sess. 74 (Ca. 2005) (statement of Francine Coeytaux, Pro-Choice Alliance for Responsible Research), *available at* http://senweb03.senate.ca.gov/committee/standing/health/PROP_71_OVERSIGHT_TRANSCRIP

Proposals to expand federal control over stem cell research to projects not supported by federal funds are also likely to prove controversial. NIH has no experience with research oversight on the scale required to enforce uniform federal guidelines, and federal rules might well conflict with state laws, regulations, and, in the case of California, covenants with bondholders. Some scientists have supported an expanded NIH role in the oversight of stem cell research while others have argued that the combination of local, state, and federal agency oversight currently in place is sufficient to ensure adequate attention to outstanding scientific, ethical, and legal questions.[59]

Proposals to dump a lot of additional federal money into stem cell research may be similarly divisive. While the recently enacted economic stimulus package contains increased funding for NIH as a whole, it seems unlikely that this increase will produce anything more than incremental funding for stem cell research, particularly hESC research. Opposition will come from the same groups that have opposed this research all along and will likely even come from elsewhere in the scientific community. After doubling between 1999 and 2003,[60] NIH's overall budget has remained flat and even declined in real terms in recent years.[61] As a result of these financial pressures, overall grant success rates have fallen from thirty percent to less than twenty percent, and as low as ten percent in some fields.[62] Scientists who are having trouble supporting their own research are likely to protest vehemently if their stem cell colleagues, who already receive money from states and private foundations, now get additional support from NIH as well. Funding for stem cell research in general, or hESC research in particular, does not have a separate budgetary identity inside NIH, but is scattered across the separate budgets of the NIH's component institutes that fund research on a range of different diseases. NIH officials in some of these institutes may find it more sensible to steer new funding away from stem cell research to other research areas that do not have substantial state or private foundation support. The odds of

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T.doc; Judy Norsigian, *Egg Donation for IVF and Stem Cell Research: Time To Weigh the Risks to Women's Health*, DIFFERENT TAKES, Spring 2005, at 1, *available at* http://www.sc.edu/healthycarolina/pdf/risksofeggdonation.pdf (statement by the Executive Director of Our Bodies Ourselves);.

59. *See* Michael Warner & Hans Smith, *Oversight from Bench to Bedside*, SCI. PROGRESS, Aug. 25, 2008, http://www.scienceprogress.org/2008/08/oversight-from-bench-to-bedside.

60. National Institutes of Health, The NIH Almanac – Appropriations, http://www.nih.gov/about/almanac/appropriations/part2.htm (last visited Apr. 30, 2009).

61. *Id.* (showing that from 2003-2007 the NIH budget increased $196 million, while keeping pace with inflation would have required an increase of $221 million).

62. For reviews of NIH's recent funding problems, see David Korn et al., *The NIH Budget in the "Postdoubling" Era*, 296 SCIENCE 1401 (2002); Joseph Loscalzo, *The NIH Budget and the Future of Biomedical Research*, 354 NEW ENG. J. MED. 1665 (2006); David G. Nathan & Alan N. Schechter, *NIH Support for Basic and Clinical Research: Biomedical Researcher Angst in 2006*, 295 JAMA 2656 (2006).

a lot of additional federal money being devoted to stem cell research seem low. Even if NIH is able to expand support for stem cell research incrementally, it will only be one payer among many, and not even the largest one.

A final factor complicating the prospects for non-incremental changes in federal stem cell policy is continued scientific uncertainty around important questions. One is the availability of alternative procedures, such as the production of induced pluripotent stem cells (iPSCs) for producing embryonic stem cell lines that do not require the destruction of embryos. The existence of alternatives to hESCs would make stem cell research much less controversial, but as discussed earlier in this Article, most stem cell scientists appear unconvinced that iPSCs are reliable substitutes.[63] While studies comparing the two are underway in several places, it seems unlikely that the political controversy around hESCs will be resolved anytime soon, particularly if iPSCs prove to be less than optimal replacements for hESCs.

Another scientific uncertainty with political consequences is the outcome of the first clinical trial of a product derived from hESCs. Almost immediately after President Obama's inauguration, the Food and Drug Administration approved an application from Geron, a California company, to begin a Phase I clinical trial of a hESC-based therapy for severe spinal cord injuries.[64] Phase I trials are only intended to gauge treatment safety, and the Geron trial will only include eight to ten patients, but it might be expected that both stem cell detractors and supporters will attempt to use the results of this trial as ammunition to support their respective positions. In short, there are both political and scientific reasons to expect incremental, rather than far-reaching, changes in federal stem cell policy and funding over the short term.

Even if stem cell supporters are successful in expanding federal hESC funding, it seems unlikely that states will diminish their funding efforts. As noted above, many states have legally obligated funds with an extended time horizon, over which it may be difficult to divert funds from their intended uses. If the NIH funding picture remains tight, scientists and universities in some states may push to institutionalize or expand state stem cell programs as an alternative source of research funding. A second factor that is likely to encourage states to persist is competition both among states and between states and several foreign countries that have begun stem cell initiatives of their own. States see themselves, at least rhetorically, as competing with one another for jobs, tax revenue, economic development, and in the case of hESC research, research talent and prestige. After the passage of Proposition 71 in California, much of the public rhetoric in support of state funding for hESC research has focused on the need for states to

63. *See, e.g.*, Hulse, *supra* note 49.

64. *See* Andrew Pollack, *F.D.A. Approves a Stem Cell Trial*, N.Y. TIMES, Jan. 23, 2009, at B1, *available at* http://www.nytimes.com/2009/01/23/business/23stem.html.

remain "competitive" and to attract or retain scientific talent and prestige.[65]

There is evidence that state efforts to make themselves more attractive to stem cell researchers through permissive rules and funding have been successful.[66] A recent report from the California Institute for Regenerative Medicine, the state agency that manages the state's stem cell initiative, claims that at least forty-five senior scientists have relocated to California from elsewhere,[67] and there is some systematic evidence that stem cell researchers have recently received more job offers than other types of scientists.[68] The Republic of Singapore, among other countries, has also mounted a highly publicized stem cell program of its own, which has recruited American and other scientists with subsidized lab space, ready access to stem cell lines, and other inducements.[69] While it is easy to overstate the effectiveness of such efforts, it seems clear that many state politicians have found concerns over "brain drains" to California or other more congenial locations to be effective arguments in pressing for state support for hESC and other forms of stem cell research.

CONCLUSION

What seems most likely, in short, is that the immediate future will be like the recent past, with the federal government being a relatively minor player and states and private funders continuing to carry the major funding and policy development burdens. hESC research will continue to be heavily supported in some states and illegal in some others, with states weighing in with hESC research funding programs of widely varying sizes. Competition among states is good for hESC research supporters—more governors and gubernatorial candidates may find it in their political interest to support state financing for this research if they can claim that state support will keep their state from "falling behind." While state financial problems may handicap state efforts to initiate or expand stem cell programs, the evidence to date suggests these programs will continue, albeit on a less well-funded basis. There will be increasingly vocal debates over royalties, product pricing, and other research management issues that will be resolved in a wide range of ways, and conflicts between the rules that apply to collaborating researchers located in different states. This system is less efficient and more administratively difficult than a single funding source and set

65. For an example of this rhetoric, see Deval L. Patrick & Therese Murray, *The Promise of Biotech*, BOSTON GLOBE, May 9, 2007, at A9.

66. *See* Levine, *supra* note 19.

67. LAURENCE BAKER & BRUCE DEAL, CIRM – INTERIM ECONOMIC IMPACT REVIEW (2008), http://www.cirm.ca.gov/pub/pdf/EcoEval_091008_rpt.pdf.

68. Aaron D. Levine, *Research Policy and the Mobility of US Stem Cell Scientists*, 24 NATURE BIOTECHNOLOGY 865 (2006).

69. For an example of the coverage of the Singapore program, see Terri Somers, *Singapore Makes Investment in its Survival*, SAN DIEGO UNION-TRIB., Dec. 18, 2006, at A1.

of rules would be, but it is an accurate reflection of the conflicting and diverse national public and political views about hESCs, which do not show any sign of going away anytime soon.

APPENDIX A. ESTIMATES OF NIH FUNDING FOR STEM CELL RESEARCH, FEDERAL FISCAL YEARS 2004 TO 2008, IN MILLIONS[70]

	FY 2004 Actual	FY 2005 Actual	FY 2006 Actual	FY 2007 Actual*	FY 2008 Estimate
Stem Cell Research Total	$553	$609	$643	$968	$938
Human Embryonic	$24	$40	$38	$74	$88
Non-Human Embryonic	$89	$97	$110	$120	$150
Human Non-Embryonic	$203	$199	$206	$226	$297
Non-Human Non-Embryonic	$236	$273	$289	$400	$497

*In FY 2007, NIH restructured its categorization of disease research. These figures are using the new structure, although NIH also released information for FY 2007 using the historical method of categorizing diseases.

70. National Institutes of Health, Research Portfolio Online Reporting Tool, http://report.nih.gov/rcdc/categories/Default.aspx (last visited Apr. 30, 2009) (noting that estimates of funding for FY 2009 and 2010 will be displayed upon transmittal of the President's budget request).

APPENDIX B. STATE GOVERNMENT SUPPORT FOR STEM CELL RESEARCH, IN MILLIONS

State	Allocated to Date	Appropriated or Authorized But Not Allocated*
California[71]	$693	$3,000
Connecticut[72]	$30	$100
Illinois[73]	$15	--
Maryland[74]	$38	$18
Massachusetts[75]	$20.2	$980
Minnesota[76]	$15	--
New Jersey[77]	$5	$280

71. California Institute for Regenerative Medicine, *supra* note 22; *Around the Regions: With State Finances Squeezed, California Stem Cell Funding Agency Eyes Contingency Plan*, BIOREGION NEWS, Jan. 5, 2009, http://www.genomeweb.com/bioregionnews/around-regions (free subscription required for access).

72. Press Release, Conn. Dep't of Pub. Health, State of Connecticut Prepares to Allocate $9.8 Million in Stem Cell Research Funds (Apr. 1, 2009) http://www.ct.gov/dph/cwp/view.asp?Q=437842&A=3659 (noting this is the third installment of grants).

73. Governor Blagojevich announced $10 million in grants in April 2006 and $5 million in August 2006. *See* Press Release, Ill. Regenerative Med. Inst., Gov. Blagojevich Announces Recipients of $5 Million in New State Stem Cell Research Funding (Aug. 17, 2006), http://www.idph.state.il.us/irmi/news_081706.html; Press Release, Ill. Regenerative Med. Inst., Gov. Blagojevich, Comptroller Hynes Announce $10 million in State Stem Cell Research Grants (Apr. 24, 2006), http://www.idph.state.il.us/irmi/news_042406.html.

74. The Maryland Stem Cell Research Fund had a budget of $15 million in FY 2007, $23 million in FY 2008 and $18 million in FY 2009. *See* Press Release, Md. Stem Cell Research Fund, Maryland Stem Cell Commission Announces that 24 Grant Agreements Have Been Signed (Jan. 22, 2008), *available at* http://www.mscrf.org/_media/client/pdf/mscrcommission/publicnotices/stemcellannualreport2007press.pdf; Press Release, Md. Stem Cell Research Fund, Maryland Stem Cell Research Commission Receives 147 Applications for Funding (Jan. 16, 2009), *available at* http://www.mscrf.org/_media/client/pdf/MSCRFApplications-AnnualReport-Final.pdf.

75. The Massachusetts Life Sciences Initiative ($1 billion) is not solely for stem cell research. *See* The Massachusetts Life Sciences Center, *supra* note 29. The Center awarded $8.2M to the University of Massachusetts for a stem cell bank and $12M in matching funds. Press Release, Univ. of Mass. Med. Sch., Massachusetts Life Sciences Center Awards $8.2 Million to UMass Medical School for Stem Cell Bank and International Registry, $12M for Matching Grants (Oct. 29, 2007), http://www.umassmed.edu/10_26_07.aspx.

76. This was a capital grant by University of Minnesota to Minnesota Stem Cell Institute. University of Minnesota, Stem Cell Institute, About Us, http://www.stemcell.umn.edu/stemcell/about/home.html (last visited Apr. 30, 2009).

77. New Jersey authorized $5 million in one round of research grants in 2005. The

State	Allocated to Date	Appropriated or Authorized But Not Allocated*
New York[78]	$118.3	--
Ohio[79]	$27.4	--

*Dashes in this column indicate that the quantity of non-allocated funds is unknown or zero.

appropriated/authorized amount includes $10 million for research grants and $270 million for stem cell lab construction. State of New Jersey Commission on Science & Technology, Stem Cell Research in New Jersey, http://www.state.nj.us/scitech/stemcell (last visited Apr. 30, 2009).

78. New York State Stem Cell Science, Grants and Contracts Awarded, http://stemcell.ny.gov/research_support_grants_awards.html (last visited Apr. 30, 2009). In November of 2008, the Health Department deferred payment of $9 million in stem cell spending. *See* Alex Philippidis, NY Gov.'s FY '10 Budget Would Cleave $5.2B from Life-Science-Related Programs, BIOREGION NEWS, Nov. 17, 2008, http://www.genomeweb.com/ bioregionnews/ny-gov%E2%80%99s-fy%E2%80%9910-budget-cuts-would-cleave-52b-life-science-related-programs (free subscription required for access).

79. Separate allocations for non-embryonic stem cell research were made in 2003 and 2006 to the Center for Stem Cell & Regenerative Medicine. National Center for Regenerative Medicine, Center for Stem Cell & Regenerative Medicine, http://www.thestemcellcenter.org (last visited Apr. 30, 2009).

APPENDIX C. EXAMPLES OF PRIVATE DONOR RESEARCH SUPPORT FOR STEM CELL RESEARCH

State	Recipient	Donors	Amount Donated (Millions)	Comments
California[80]	California Institute for Regenerative Medicine (CIRM); various universities	Variety of foundations and individual donors	$955	
California[81]	CIRM	Bond anticipation notes "purchased by foundations and private parties"	$45	Proceeds used for research grants; repaid from bond proceeds
Maryland[82]	Johns Hopkins University	Michael Bloomberg	$100	Amount for hESC research is unclear

80. *See, e.g.*, LAURENCE BAKER & BRUCE DEAL, ANALYSIS GROUP, CIRM – INTERIM ECONOMIC IMPACT REVIEW, ADDENDUM 1: ECONOMIC EFFECT OF CIRM FACILITIES AND EQUIPMENT GRANTS ON TAX REVENUES AND JOBS (SEPTEMBER 10, 2008), *available at* http://www.cirm.ca.gov/pub/pdf/EcoEval_091008_Addendum.pdf; Richard C. Paddock, Broads Donate $25 Million for Stem Cell Research Lab, L.A. TIMES, Dec. 18, 2008, at B3; Terri Somers, *Donations Add Muscle to Bid for Stem Cell Institute Funds*, SAN DIEGO UNION-TRIB., Feb. 29, 2008, at C-1; Richard C. Paddock, *Broads Donate $25 Million for Stem Cell Research Lab*, L.A. TIMES, Dec. 18, 2008, at B3; Terri Somers, *Stem-Cell Researchers Celebrate $30 Million Donation*, SAN DIEGO UNION-TRIB., Sept. 16, 2008, http://www.signonsandiego.com/news/metro/20080916-1858-bn16stems.html; Oliver Staley, Stanford Gets $75 Million for Stem Cells Research from Lokey, BLOOMBERG.COM, Oct. 6, 2008, http://www.bloomberg.com/apps/news?pid=20601103&sid=aH.JjGHbrwA4&refer=us; *UCSF Snags $25 Million Stem Cell Donation*, California Stem Cell Report, Dec. 18, 2008, http://californiastemcellreport.blogspot.com/2008/12/ucsf-snags-25-million-stem-cell.html.

81. BAKER & DEAL, *supra* note 67, at 9.

82. Sonya Geis, *Rich Donors Help Calif. Fund Stem Cell Research*, WASH. POST, Dec. 19, 2006, at A2, *available at* http://www.washingtonpost.com/wp-dyn/content/article/2006/12/18/AR2006121801080.html (noting that this donation was "largely for stem cell research"); Winnie Hu, *New York: Bloomberg Donates $100 Million to University*, N.Y. TIMES, Feb. 3, 2006, at B4.

State	Recipient	Donors	Amount Donated (Millions)	Comments
Maryland[83]	Johns Hopkins University Institute for Cell Engineering	Anonymous donor	$58.5	
Massachusetts[84]	Harvard Stem Cell Institute	Howard Hughes Medical Institute; Juvenile Diabetes Research Foundation; Harvard; other philanthropists	$40	$100 million target[85]
Massachusetts[86]	Funds provided in conjunction with state life sciences initiative	Unspecified	$250	Unclear if donations already made or contingent on state support
Massachusetts[87]	Two Harvard professors: Kevin Eggan and Chad Cowan	Stowers Medical Institute	$10	
Missouri[88]	Stowers Medical Institute	James and Virginia Stowers	$2,000	Unrestricted donation of stock and cash reserve

83. Press Release, Johns Hopkins Univ. Sch. of Med., Hopkins Launches Cell Engineering Institute with $58.5 M. Gift (Jan. 30, 2001), *available at* http://www.hopkinsmedicine.org/press/2001/JANUARY/010130.HTM.

84. HARVARD STEM CELL INST., CONNECTIVITY: HARVARD STEM CELL INSTITUTE ANNUAL REPORT 32 (2006), *available at* http://www.hsci.harvard.edu/files/HSCI_Annual_Report_2006.pdf.

85. *Campaigning for Stem Cells*, NEW ATLANTIS, Spring 2004, at 93, 94; *Harvard Stem Cell Studies Raise Eyebrows*, FOXNEWS.COM, Apr. 12, 2005, http://www.foxnews.com/story/0,2933,153130,00.html.

86. Commonwealth of Massachusetts, *supra* note 47, at 2 (projecting "$250 million in private sector matching funds for capital, research grants, fellowships, and workforce training").

87. *See* Constance Holden, *States, Foundations Lead the Way After Bush Vetoes Stem Cell Bill*, 313 SCIENCE 420 (2006).

88. Stowers Institute for Medical Research, Fact Sheet, http://www.stowers-institute.org/MediaCenter/docs/FactSheet.pdf (last visited Apr. 30, 2009).

State	Recipient	Donors	Amount Donated (Millions)	Comments
New York[89]	The Rockefeller University; Weill Medical College of Cornell University; Memorial Sloan-Kettering Cancer Center	Starr Foundation	$50	
New York[90]	Rockefeller University	Harriet Heilbrunn	$5	
New York[91]	Memorial Sloan-Kettering Cancer Center	Geoffrey Beene, LLC	$101.9	Total donations including company shares; funds not specifically allocated to stem cell research
New York[92]	Mount Sinai School of Medicine—Black Family Stem Cell Institute	Leon D. Black	$10	

89. Press Release, Mem'l Sloan-Kettering Cancer Ctr., Stem Cell Research in New York City Receives Pivotal Boost from The Starr Foundation (May 23, 2005), http://www.mskcc.org/mskcc/html/57616.cfm.

90. Press Release, Rockefeller Univ., Rockefeller University Establishes Stem Cell Research Center (Aug. 3, 2004), http://runews.rockefeller.edu/index.php?page=engine&id=42.

91. Press Release, Mem'l Sloan-Kettering Cancer Ctr., New Geoffrey Beene Gift to Memorial Sloan-Kettering Puts Total Support Over $100 Million (Oct. 9, 2008), http://www.mskcc.org/mskcc/html/87852.cfm.

92. *Mount Sinai School of Medicine Establishes Stem Cell Institute*, MED. NEWS TODAY, May 6, 2005, http://www.medicalnewstoday.com/articles/23926.php.

State	Recipient	Donors	Amount Donated (Millions)	Comments
New York[93]	Columbia University Medical Center	Various private philanthropists	$25	Total $50 million goal
New York[94]	Weill-Cornell's Ansary Center for Stem Cell Therapeutics	Shahla and Hushang Ansary	$15	
New York[95]	Post-doctoral research fellows	New York Stem Cell Foundation (supported by Stanley and Fiona Druckenmiller, The Shelley & Donald Rubin Foundation, and an anonymous donor)	$5	Foundation also established a "safe haven" lab
New York[96]	University of Rochester	Jack Erdle	$1	

93. Press Release, Columbia Univ. Med. Ctr., Columbia University Medical Center Launches Multi-Year Campaign To Support Stem Cell Research (June 15, 2005), http://www.cumc.columbia.edu/news/press_releases/stem_cell_initiative.html.

94. Robert Kolker, *The California Stem-Cell Gold Rush*, N.Y. MAG., Dec. 27, 2004, *available at* http://nymag.com/nymetro/health/features/10755/index3.html.

95. Press Release, New York Stem Cell Found., The New York Stem Cell Foundation Commits More than $5 Million in Fellowships for New York Scientists Engaged in Human Embryonic Stem Cell Research (June 28, 2007), *available at* http://www.nyscf.org/images/pdf/pr_fellowship_07_28_07.pdf; *see also* The New York Stem Cell Foundation, Fellowships & Grants, http://www.nyscf.org/fellowshipsgrants/fellowships_grants.html (last visited Apr. 30, 2009).

96. Press Release, Univ. of Rochester Med. Ctr., Medical Center Receives Gift for Stem Cell Research (Aug. 10, 2006), http://www.urmc.rochester.edu/PR/news/story.cfm?id=1201.

State	Recipient	Donors	Amount Donated (Millions)	Comments
New York[97]	Albert Einstein College of Medicine Yeshiva University	Ruth and David Gottesman	$15	
Texas[98]	University of Texas Health Sciences Center at Houston	Anonymous patient	$25	
Washington[99]	University of Washington Stem Cell Institute	Multiple donors	$17	$100 million campaign[100]
Wisconsin[101]	University of Wisconsin	Wisconsin Alumni Research Foundation (WARF)	$50	WARF is the primary investor in embryonic stem cell research in Wisconsin

97. Albert Einstein College of Medicine, Einstein Receives $25-Million Gift to Support Stem Cell and Epigenomic Research and Clinical Skills Training, http://www.aecom.yu.edu/home/fullstory.asp?id=198 (last visited Apr. 30, 2009) (noting that "$15 million will be used to establish the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research"); *see also* New York City Bioscience Initiative, Funding for Stem Cell Research, http://www.nycbiotech.org/stem_cell.html (last visited Apr. 30, 2009).

98. Amber Buckley, *Anonymous Donor Pledges $25 Million to Stem Cell Research*, DISTINCTIONS (Univ. Tx. Health Sci. Ctr., Houston, Tx.), May 2004, http://publicaffairs.uth.tmc.edu/distinctions/archive/2004/May/25.html.

99. *See* Tom Paulson, *Private Funds Keep Stem Cell Research Viable in Seattle*, SEATTLE POST-INTELLIGENCER, Sept. 29, 2007, at A1, *available at* http://www.seattlepi.com/local/333633_stemcells29.html.

100. Estimates of the amount sought by the University of Washington campaign vary between $50 million, *id.*, and $100 million, Eric Engleman, *$100M Stem-Cell Push: UW Counters Rivals*, PUGET SOUND BUS. J., Mar. 10-16, 2006, at 1.

101. *See* Tom Still, *Wisconsin's Private Funding of Stem Cell Research Bucks Coastal Models*, WIS. TECH. NETWORK NEWS, Sept. 8, 2008, http://wistechnology.com/articles/5003.

Federal Funding and the Regulation of Embryonic Stem Cell Research: The Pontius Pilate Maneuver

Robert J. Levine*

> So when Pilate saw that he could do nothing, but rather that a riot was beginning, he took some water and washed his hands before the crowd, saying, "I am innocent of this man's blood; see to it yourselves."[1]

In this volume, my colleagues have presented a comprehensive account of the pros and cons of stem cell research and cloning; I will not repeat this discussion, nor will I focus on my own views regarding the moral acceptability of these activities.[2] Instead, I plan to focus on the typical response of the federal government to issues of the type that are presented by embryonic stem cell research and cloning and to evaluate the consequences of this typical response.

The issues to which I refer are, in general, features of much research in the field of reproductive biology. The issues arise when a particular project or a field of research or practice entails either the creation by any means other than

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1. *Matthew* 27:24.

2. My position on the moral acceptability of various types of stem cell research is, in general terms, as follows: Any statement on the moral acceptability of human stem cell research presupposes that particular research proposals conform to all relevant standards for the ethical justification of research involving humans as subjects. I believe that it is morally acceptable to perform any and all types of stem cell research when there is no plan to create or use cells having the potential to become a human person. Plans to use or create cells having the potential to become a human person are ethically more problematic. I do not regard as decisive the distinction between human embryos created for research purposes and human embryos created for procreative or other non-research purposes (e.g., "leftover" embryos created *in vitro* with the aim of achieving pregnancy). In deference to those who regard this distinction as important, however, I would support a requirement that creation of such cells for research purposes be limited to those cases in which the research objective cannot be realized using cells created for non-research purposes. Finally, I would favor the specification of a maximum permissible stage of development for embryos that are destined to be used for research purposes; precedents in the US favor the identification of fourteen days as the maximum permissible stage of development. I would be willing to consider allowing further development in some cases. The details of my positions and arguments supporting them are beyond the scope of this discussion.

"natural procreation" of an entity that could develop into a human person, or the destruction of such an entity, whether the entity was created "naturally" or *in vitro*. Embryonic stem cell research includes both problematic procedures: the creation of embryos via in vitro fertilization (IVF) or cloning, and the derivation of cell lines (necessitating the destruction of the potential for an embryo to develop into a person). Cell lines created from so-called "adult" stem cells do not fall under this category because an "adult" stem cell cannot develop into a human person.[3] Federal officials would strongly prefer not to alienate those who believe destruction of embryos that could develop into human persons is murder (notably, but not exclusively, the religious right) or that the creation of human life by artificial means is morally wrong. They similarly do not want to appear to oppose the efforts of scientists to pursue cures for deadly or disabling diseases, particularly when the means to pursue such cures are advocated aggressively by popular public figures.

The federal official who must produce a policy to govern such fields of research or practice appears to be ensnared in a true dilemma. To choose either side is fraught with grave political risk. In such circumstances, the official can, and often does, make a "safe" decision, choosing neither side in this controversy. The safe decision is to *permit* the conduct of the activity in the private sector while withholding the support of public funding for the field of study or practice. The official, like Pontius Pilate, washes his or her hands of the matter.

On the occasion of announcing such a decision, the official takes note of the great benefits that could be developed through the proposed research. The official also observes that there are citizens who reject the proposal on moral grounds. On the one hand, the decision allows the development of the new technology in the private sector. Those who wish to develop it are thus free to do so, and those who wish to benefit from it after development are free to purchase it. On the other hand, those who oppose the development on moral grounds are also treated with respect. They are not forced to contribute through taxes to a development they find immoral. Some of those in the latter group may protest that the government should go further—for example, that it should act affirmatively to rule out the destruction of human embryos, equated with the murder of unborn children. The standard response to these protests is that the U.S. Supreme Court removed this decision from the executive or legislative branches in *Roe v. Wade*.[4] It is commonly said that the Supreme Court has ruled that the

3. The President's Council on Bioethics discusses research on the possibility that adult cells could be dedifferentiated or reprogrammed back to a totipotent state and thus, if implanted, capable of developing into an entire organism. *See* PRESIDENT'S COUNCIL ON BIOETHICS, ALTERNATIVE SOURCES OF HUMAN PLURIPOTENT STEM CELLS 51 (2005), *available at* http://www.bioethics.gov/reports/white_paper/alternative_sources_white_paper.pdf.

4. The Supreme Court in *Roe v. Wade* made it clear that under the laws of the United States, a "person," with all the rights attaching to that status, is a live-born human capable of life apart from

government may not unduly burden a woman seeking an abortion, even if she gives no reason to justify it.[5] It seems even more difficult to intervene when embryonic cells are destroyed for a health-promoting reason such as research on therapies. With the passage of the Dickey-Wicker Amendment in the mid-1990s,[6] and bolstered by presidential actions in the Bush Administration,[7] federal action regarding embryonic stem cell research has become a classic example of hand-washing. Although the policy landscape has changed somewhat under the Obama Administration,[8] it remains to be seen whether new federal funds and regulation will actually be devoted to stem cell research involving human embryos.

In this Article, I will investigate the implications of this federal habit of evading policy decisions that either support or prevent advances in the field of reproductive biology. Part I will examine the history of federal fund withholding, outlining the statutory and executive interventions that contributed to this system. Part II will explore the ways that embryonic stem cell researchers and many of their colleagues interact with federal regulations on research, particularly regulation by the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS). Finally, Part III will outline some of the recent consequences of past withholding of federal funds.

I. A BRIEF HISTORY OF WITHHOLDING OF FEDERAL FUNDS FROM EMBRYONIC STEM CELL RESEARCH

Since 1973, the year of the *Roe v. Wade* decision, the federal government has decided to withhold federal funding for the support of many research or

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the body of his or her mother. Roe v. Wade, 410 U.S. 113, 163 (1973) ("With respect to the State's important and legitimate interest in potential life, the 'compelling' point is at viability."). Since that decision, executive or legislative attempts to declare frozen stem cells to be "persons" in circumstances where they will never be positioned to become live-born humans seem in direct conflict with the jurisprudence of *Roe*. Additionally, since the pregnant woman has the right to make decisions about her fetus, she would certainly seem to have the right to make decisions about the cells that would make up that fetus. As a recent article demonstrates, most couples who have stored frozen embryos opt for their use in research over any other method of disposal. Anne Drapkin Lyerly & Ruth R. Faden, *Embryonic Stem Cells: Willingness To Donate Frozen Embryos for Stem Cell Research*, 317 SCIENCE 46, 47 (2007).

5. Roe v. Wade, 410 U.S. 113 (1973); *see also* Planned Parenthood of Se. Pa. v. Casey, 505 U.S. 833 (1992).

6. Balanced Budget Downpayment Act of 1996, Pub. L. No. 104-99, §128, 110 Stat. 26, 34 (1996).

7. Exec. Order No. 13,435, 72 Fed. Reg. 34,591 (June 22, 2007); Press Release, Office of the Press Sec'y, White House, President Discusses Stem Cell Research (Aug. 9. 2001), *available at* http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html.

8. *See* Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

service activities in the field of reproductive biology. It has been particularly restrictive of those activities that are designed either to create an entity that could develop into a human person by any means other than "natural procreation" or to destroy such an entity whether it was created "naturally" or *in vitro*. Among the activities that have had their federal support terminated, forbidden, or suspended by federal legislation or executive order are *in vitro* fertilization, fetal research, therapeutic transplantation of tissues derived from human fetal tissue, and cloning of humans.[9] The most recent example was President George Bush's first use of his veto power in July of 2006 to block the enactment of H.R. 810, the Stem Cell Research Enhancement Act of 2005.[10]

Within a year of the *Roe v. Wade* decision, Congress passed the National Research Act,[11] Title II of which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission).[12] This legislation was enacted in response to public concern over multiple reports of abuses in research involving human subjects. One of the exposés of abuse in this field concerned research on "newly delivered live fetuses . . . before they died."[13]

Two provisions in the Congressional mandate to the Commission signaled the high priority assigned by Congress to addressing the ethical problems presented by proposals to perform research on fetuses.[14] Firstly, in an act that allotted two years to a comprehensive investigation of all research involving human subjects, Congress directed the Commission to report on research on the fetus within four months.[15] Secondly, pending receipt of this report, Congress imposed its only moratorium on the conduct or support by the Department of Health, Education, and Welfare of all "research . . . on a living human fetus, before or after the induced abortion of such fetus, unless such research is done

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9. *See, e.g.*, John Garvish, *The Clone Wars: The Growing Debate over Federal Cloning Legislation*, 2001 DUKE L. & TECH. REV. 0022, http://www.law.duke.edu/journals/dltr/articles/2001dltr0022.html (discussing proposed regulation of research involving human cloning).

10. Press Release, Office of the Press Sec'y, White House, Message to the House of Representatives (July 19, 2006), *available at* http://georgewbush-whitehouse.archives.gov/news/releases/2006/07/20060719-5.html; *see also* Stem Cell Research Enhancement Act of 2005, H.R. 810, 109th Cong. (2005).

11. National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974) (codified at 42 U.S.C. § 289*l*-1) (repealed).

12. *Id.*; *see also* ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 297 (2d ed. 1988).

13. *See* ALBERT R. JONSEN, THE BIRTH OF BIOETHICS 94 (1998).

14. *See* John C. Fletcher & Joseph D. Shulman, *Fetal Research: The State of the Question*, HASTINGS CENTER REP., Apr. 1985, at 6, 6 (1985); Robert J. Levine, *Symposium on Definitions of Fetal Life*, 23 CLINICAL RES. 103, 103 (1975).

15. National Research Act, Pub. L. No. 93-348, § 202(3)(B), 88 Stat. 342, 350 (1974).

for purposes of assuring the survival of such fetus."[16]

Very similar language was chosen fourteen years later by the Assistant Secretary for Health when he imposed a ban on the conduct of another category of research on the human fetus: "The Assistant Secretary for Health, Department of Health and Human Services, is instituting a moratorium, effective immediately, on research funded by the Public Health Service (PHS) utilizing human fetal tissue, obtained from induced abortions, for therapeutic transplantations."[17] It is worth noting that the language chosen by Congress and by the Assistant Secretary contains an implicit acknowledgement of the limits of the federal government's constitutional authority to regulate. In the field of research involving human subjects, the authority to regulate activities for which the federal government provides funding in the form of grants or contracts is established by the "conditional spending power" provisions of the Constitution.[18] Similarly, the regulatory power of the FDA is established by the constitutional authority to regulate interstate commerce. According to the Tenth Amendment, "The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people."[19]

There is one apparent substantive difference between the targets of the two moratoria. In its charge to the National Commission, by specifying that its moratorium applies only to the living human fetus, Congress suggested that its primary concern was for the well-being of the individual fetus. This was also reflected in its exclusion from the moratorium of "research . . . done for purpose of assuring the survival of such fetus."[20] The Assistant Secretary, by specifying that the moratorium applied only to "induced abortion," as distinguished from spontaneous abortions (or miscarriages), seemed primarily concerned with the moral legitimacy of induced abortions.[21]

These apparent differences notwithstanding, the arguments presented by those who opposed fetal research in both cases focused on the morality of abortion, which was discussed as indistinguishable from the destruction of human embryos. Abortion was portrayed as murder of an innocent child. The conduct of research on fetuses or on their tissues was characterized as lending legitimacy to the "abortion industry," as providing incentives to women to have abortions, and as a revealing conspiracy of physicians and researchers to increase the supply of "research material." The conduct of research on the fetus was

16. *Id.* § 213, 88 Stat. at 353.

17. NAT'L INSTS. OF HEALTH, NIH GUIDE FOR GRANTS AND CONTRACTS (1988), *available at* http://grants.nih.gov/grants/guide/historical/1988_05_09_Vol_17_Special_Notice.pdf.

18. U.S. CONST. art I, § 8, cl.1.

19. U.S. CONST. amend. X.

20. National Research Act, Pub. L. No. 93-348, § 213, 88 Stat. 342, 353 (1974).

21. *Id.*

portrayed as material cooperation in an evil act. The proponents of fetal research, in addition to presenting the benefits that could be realized through the conduct of such research, directed much of their energy toward refuting their opponents' claims. They concentrated particularly on rejecting their opponents' claims about the moral status of the fetus at various stages of its development.[22]

Research and any derived therapies that utilize stem cell lines created from embryos, whether cloned or created by *in vitro* fertilization, evoke similar concerns. That is, those who oppose the *in vitro* creation or use of embryos for research purposes characterize this research as legitimizing these practices. Under current regulations, however, given Congressional restrictions still in force,[23] the creation of new embryos for research is not permissible with federal funding. While there is no explicit "ban" on embryo research, and while federal funds can now support research on existing lines or lines derived without federal funding,[24] the use of federal funding to create new cell lines remains prohibited through the Dickey-Wicker Amendment of 1995 since its passage.[25] This amendment has been carried over through NIH appropriations acts every year since. This amendment indicates that, in research supported by federal funds, embryos cannot be created for research purposes or "destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero*" in other federally funded research.[26] That is,

22. There are several collections of references on this topic. For an early overview, see LEVINE, *supra* note 12, at 299. Collections of papers may also be found in DEP'T OF HEALTH, EDUC., & WELFARE, APPENDIX: RESEARCH ON THE FETUS (1976) and *Human Fetal Tissue Transplantation Research Panel: National Institutes of Health*, *in* SOURCE BOOK IN BIOETHICS: A DOCUMENTARY HISTORY 103 (Albert R. Jonsen, Robert M. Veatch & LeRoy Walters eds., 1998).

23. *See* Sheryl Gay Stolberg, *New Stem Cell Policy To Leave Thorniest Issuse to Congress*, N.Y. TIMES, Mar. 9, 2009, at A1.

24. *Id.*; *see also* Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

25. Balanced Budget Downpayment Act of 1996, Pub. L. No. 104-99, §128, 110 Stat. 26, 34 (1996).

26. *See, e.g.*, OFFICE OF MGMT. & BUDGET, BUDGET OF THE UNITED STATES GOVERNMENT, FISCAL YEAR 2005, Appendix § 510, at 735-36, *available at* http://georgewbush-whitehouse.archives.gov/omb/budget/fy2005/pdf/appendix/lab.pdf. Such language has appeared in the appropriations bills each year since FY 2002. In his State of the Union Address in January 2008, President Bush reasserted his determination to ban the use of federal funds to do research on embryonic stem cells:

> On matters of life and science, we must trust in the innovative spirit of medical researchers and empower them to discover new treatments while respecting moral boundaries. In November, we witnessed a landmark achievement when scientists discovered a way to reprogram adult skin cells to act like embryonic stem cells. This breakthrough has the potential to move us beyond the divisive debates of the past by extending the frontiers of medicine without the destruction of human life.

Press Release, Office of the Press Sec'y, White House, President Bush Delivers State of the Union Address (Jan. 28, 2008), *available at* http://georgewbush-whitehouse.archives.gov/news/

research must either promote or at least avoid shortening the life of the embryo. Accordingly, creating embryos for research purposes and deriving embryonic stem cell lines from embryos are not permitted.

After his August 9, 2001 announcement,[27] which limited the permissibility of embryonic stem cell research, President Bush decided to retain the language of the Dickey Wicker Amendment. Further, Bush chose to add language governing funds for research on stem cell lines already created.[28] The "bad deeds" of creating embryos through IVF and then destroying embryos were already done in the private sector, but the public sector could reap the benefits of stem cell research. Any cloning technology used to create stem cells of course would have to be in the private sector, if it was not explicitly banned by state laws. President Bush reaffirmed these restrictions in July of 2006 when he vetoed the Stem Cell Research Enhancement Act of 2005.[29] Without further Congressional action to overturn the Dickey-Wicker Amendment, this funding structure will persist to some extent despite President Obama's recent executive order;[30] although federal funds may now support research on all existing stem lines and those yet to be derived with non-federal funding, researchers may not use federal money to create new lines.

II. FEDERAL REGULATION OF RESEARCH INVOLVING HUMAN SUBJECTS

Research designed to develop novel therapeutic, diagnostic, or preventive agents (hereafter called "therapies") is generally regulated by the federal Food

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releases/2008/01/20080128-13.html.

27. Press Release, Office of the Press Sec'y, White House, President Discusses Stem Cell Research (Aug. 9. 2001), *available at* http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html.

28. For one example of Bush's support, see Office of Management & Budget, S. 1536 – Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Bill, FY 2002, Oct. 30, 2001, http://georgewbush-whitehouse.archives.gov/omb/legislative/ sap/107-1/S1536-s.html:

> The President strongly believes that the Dickey-Wicker Amendment, which for years has ensured that the federal government observes important ethical boundaries at the same time that it provides support for scientific research, should not be altered. The Administration therefore strongly opposes the Senate version of the bill, which modifies the existing language and would signal a weakening of the Federal Government's commitment to protecting human embryos. The Administration strongly supports the House version of the bill, which retains the current language, and includes clarifying report language that is consistent with the President's August 9, 2001 announcement. The President's senior advisors would recommend that he veto the bill if it contains the Senate's language.

29. Message to the House of Representatives Returning Without Approval the "Stem Cell Research Enhancement Act of 2005," 42 WEEKLY COMP. PRES. DOC. 1365 (July 19, 2006).

30. Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

and Drug Administration.[31] Research designed to evaluate the safety and efficacy of the novel product must be carried out according to an orderly set of protocols as specified in the regulations and guidelines of the agency (phases I, II, and III). Each of the specific protocols must be reviewed and approved by an Institutional Review Board (IRB) before the research may be initiated. There are detailed regulations specifying protections of the rights and welfare of the research subjects including provisions for negotiating and documenting informed consent. The IRB must determine that the burdens and benefits of research are distributed equitably. The sites of the research are subject to monitoring by agents of the FDA to ensure compliance with the regulations. Other regulations of the FDA authorize inspections of the laboratories in which some aspects of the research are carried out along with quality control activities directed at the manufacture and distribution of the product. Finally, the FDA has the authority to determine if and when regulated "test articles" (novel therapies) may be licensed for commercial distribution. The approval of a "New Drug Application" or a "marketing permit" occurs only after the FDA determines that the product is safe and that its efficacy has been established by trials recognized as adequate and well-controlled.

The FDA does not have jurisdiction over all research designed to develop novel therapies. As noted earlier, the scope of its authority is limited to interstate commerce. Some novel therapies are not products that will be entered into interstate commerce. Notable among these are surgery and "talking psychiatry."

The development and use of some drugs and "biologicals" has taken place entirely within the borders of a single state, and recent state initiatives to fund stem cell research suggests this may become more common.[32] An interesting and highly publicized case in point was the Biotherapeutics Corporation developed in the state of Tennessee by Dr. Robert Oldham and his colleagues.[33] The novel therapies it developed for its patients were not subject to FDA regulation because they were not shipped across state lines. Many of the patients traveled across state lines to get to Tennessee where individualized therapy was made available for them. This was entirely a fee-for-service program and it was not covered by insurance. Criticism was primarily directed at the fact that none but the relatively wealthy could afford this individualized therapy; some commentators also expressed concern that the products employed by Biotherapeutics had not been shown to be safe and effective.

Therapies derived from embryonic cell lines, including those derived from

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31. For an overview of FDA regulations, see LEVINE, *supra* note 12; and ISLAT Working Group, *ART into Science: Regulation of Fertility Techniques*, 281 SCIENCE 651 (1998).

32. *See* James W. Fossett, *Beyond the Low-Hanging Fruit: Stem Cell Research Policy in an Obama Administration*, 9 YALE J. HEALTH POL'Y L. & ETHICS 523 (2009).

33. *See* Paul Cotton, *Treatments of Last Resort?*, 17 HARV. HEALTH LETTER 9 (1991); Steven Flax, *Leading-Edge Cancer Treatments for Sale,* FORTUNE, Feb. 17, 1986, at 77.

cell lines available for federally-funded research, would fall under the FDA regulations insofar as they were intended for use in humans.[34] However, it is conceivable that for therapies derived from cloning, interstate commerce need not necessarily take place. Just as in the Oldham case, all the necessary materials could be developed and utilized within the confines of a single state. Other therapies developed from existing embryonic stem cell lines, or from a "universal" cell line if and when it is created, could have interstate uses and, if so, would be regulated by the FDA.

The federal government also has the authority and responsibility to regulate research and health care practices that are funded at least partially by the federal government. In the field of health care research, most of the funding is in the form of grants and contracts from HHS. The federal regulations for the protection of human subjects for almost all federally-funded research are called the Common Rule;[35] its provisions for IRB review and informed consent are substantially similar to those in the FDA regulations. In addition, all applications for federal funds to support research must be reviewed and approved by committees of experts to determine that they are scientifically meritorious and that the researchers have the requisite skills and facilities to perform the research successfully; at the NIH, for example, these committees are called Initial Review Groups (IRG) or Study Sections. After review by the IRG, the applications must also be reviewed by advisory bodies to determine, among other things, whether they match the priorities of the funding institute.

All institutions that receive federal funding to support the conduct of research involving human subjects are required to file an "assurance" with the federal Office for Human Research Protection (OHRP) that they will comply with the federal regulations for the protection of human research subjects.[36] Although the authority of the federal government to regulate research is limited by the Constitution to those activities for which it provides funding or that will produce products for interstate commerce, OHRP requests that institutions receiving such funding promise "voluntarily" to apply the requirements of these regulations to all research carried out within the institution. This is accomplished by adding a commitment to do so to their statements of assurance. Most, but not all, institutions do this.

The voluntary agreement by most research institutions to extend the

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34. OFFICE FOR HUMAN RESEARCH PROT., DEP'T HEALTH & HUMAN SERVS., GUIDANCE FOR INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS REGARDING RESEARCH INVOLVING HUMAN EMBRYONIC STEM CELLS, GERM CELLS AND STEM CELL-DERIVED TEST ARTICLES 2 (2002), *available at* http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf (noting that "cells or test articles regulated as drugs, devices, and biological products" are "subject to FDA regulations").

35. 45 C.F.R. § 46 (2008). For an overview of DHHS regulations and the Common Rule, see Levine, *supra* note 12.

36. 45 C.F.R. § 46.103 (2008).

applicability of the Common Rule to all research conducted within the institution has the good effect of ensuring, for example, that all research conducted within the institution will be reviewed by an IRB and that informed consent will meet the federally mandated standards. However, the effects of such voluntary compliance in the field of assisted reproductive technology (ART) are difficult to assess. Lack of federal (or other external) funding serves as a disincentive to some university hospitals or other research institutions to allow such research and development activities within the institution; particularly in the early stages of development, the institutions may lack confidence that they will recover the costs of the development without subsidy. Moreover, many researchers (and not just those who are unethical or unscrupulous) would likely prefer to carry out their research and practice activities in clinics that receive no federal research funds and other settings that are beyond the reach of increasingly burdensome human subject protection bureaucracies.[37]

III. CONSEQUENCES OF WITHHOLDING OF FEDERAL FUNDING

When the federal government withholds or withdraws funding from a field of research, there are often consequences that adversely affect the rights and welfare of the people. This is particularly problematic when the research is designed to develop a therapeutic intervention that is not covered by FDA regulations. In short, all of the checks and balances mentioned earlier in this paper are likely to be absent.

ART is a field of research and practice that serves as a good case study for evaluating the adverse consequences of withholding federal funding for a field of research designed to develop therapeutic interventions. In her excellent brief overview of the regulation (or lack thereof) of ART, Rebecca Dresser begins by noting that "[r]eferences to the 'Wild West' of infertility treatment are common."[38] Dresser summarizes the main features of the problem as follows:

> Because novel ART procedures are not covered by the FDA approval process that governs drugs and other medical products, ART procedures need not meet FDA safety and efficacy standards before entering the clinical arena. The National Institutes of Health and other federal agencies rarely support research relevant to ART; thus, innovative approaches may be tried in the clinical setting without prior research ethics review. Because insurance coverage for ART is quite limited, reimbursement requirements fail to promote quality care. Moreover, because ART interventions may be performed outside hospital

37. Norman Fost & Robert J. Levine, *The Dysregulation of Human Subjects Research*, 298 JAMA 2196 (2007); Robert J. Levine, *Institutional Review Boards: A Crisis in Confidence*, 134 ANNALS INTERNAL MED. 161 (2001).

38. Rebecca Dresser, *Regulating Assisted Reproduction*, HASTINGS CENTER REP., Nov.-Dec. 2000, at 26, 26.

> settings, hospitals are not able to screen out unqualified practitioners. Last, the malpractice system's ability to stimulate quality care is weakened by difficulties in proving negligence, causation, and harm on behalf of patients who fail to have children or have children with health problems.[39]

Lack of IRB review in the field can have many additional consequences. For example, the research may proceed without "independent" assessment of the risks and benefits of participation. Procedures for obtaining and documenting informed consent may fall short of standards federally mandated under the Common Rule and corresponding FDA guidelines. Research may also proceed without assurance that there is equitable distribution of its burdens and benefits, undermining established duties of justice, beneficence, and nonmaleficence. With regard to the latter, owing to the lack of external funding, even during the "investigational" stage, the interventions are most likely to be tested on patients who can pay for them. Subsequently, owing to the lack of insurance coverage, the use of such procedures is generally limited to the relatively wealthy who can finance these therapeutic interventions out-of-pocket.[40]

Lack of FDA involvement means that there is no monitoring for compliance with FDA standards for, among other things, high-quality laboratory services. Moreover, unsupervised research lacks an enforceable standard for determining whether and when it is appropriate to move out of the investigational stage to make a technology available as part of the routine and accepted practice of medicine.[41] Lack of federal funding also removes the various review policies and procedures designed to ensure both high quality in research methodologies and facilities and the competence of the investigators.

There are some federal regulations concerned with ART.[42] For example, federal law requires IVF programs to report their treatment success rates to the Centers for Disease Control and Prevention (CDC), which publishes these data annually. The Federal Trade Commission has issued "cease and desist" orders to several IVF clinics whose advertisements misrepresented their success rates. The FDA is developing rules to screen sperm, egg, and embryo donors for communicable diseases. The CDC has developed standards for labs and professionals performing ART services and some states are considering incorporating them into law. In general, however, these regulatory activities stop far short of providing the level of protection for subjects and patients that is customary for those therapeutic interventions that are either regulated by the

39. *Id.* at 27.

40. *See, e.g.*, Neil Davis, *The Constitutionality of Fetal Experimentation Statutes: The Case of* Lifchez v. Hartigan, 25 J. HEALTH & HOSP. L. 37 (1992); Dresser, *supra* note 38, at 27.

41. *See* Jason Christopher Roberts, *Customizing Conception: A Survey of Preimplantation Genetic Diagnosis and the Resulting Social, Ethical and Legal Dilemmas*, 2002 DUKE L. & TECH. REV. 0012.

42. *See* Dresser, *supra* note 38.

FDA or funded by the federal government.[43]

CONCLUSION

When a field of research or a particular project entails either the creation by any means other than "natural procreation" of an entity that could develop into a human person or the destruction of such an entity, whether the entity was created "naturally" or *in vitro*, it usually incites strong controversies. These controversies are particularly strident when the purpose of the research is to develop products or procedures intended to cure, prevent or relieve lethal or disabling diseases. Those who make policy are presented with a choice between two politically undesirable alternatives. They may side with those who oppose the research, a stance which will be attacked as callous disregard for the well-being of afflicted persons. Or, they may side with those who advocate for the research and be branded as evil in that they condone the murder of innocent babies.

Politicians often evade such criticism by making a safe decision in which they do not take a side. I refer to such a decision as the Pontius Pilate Maneuver: the decision-maker figuratively washes his or her hands of a difficult problem so as to avoid alienation of either of the disputing constituencies. The safe decision is to permit the conduct of the activity in the private sector while withholding the support of public funding for the field of study or practice. The decision has the effect of allowing the development of the new technology in the private sector. Those who wish to develop it are thus free to do so and those who wish to benefit from it once it is developed are free to purchase it. On the other hand, those who oppose the development on moral grounds are also treated with respect. They are not forced to contribute (through their taxes) to a development they find immoral.

Such a decision may have serious consequences that impact both the rights and welfare interests of research subjects and the patients who might be treated with the new product or procedure once it is developed. The withholding of federal funding limits the authority of the federal government to engage in many of its activities that are designed to protect the rights and interests of research subjects and patients. If, as in the case of embryonic stem cell research, the technology that is not a new drug or other therapeutic product that will be introduced in interstate commerce, the FDA has no authority to regulate its development and subsequent introduction into the practice of medicine. Thus, the research and therapeutic use of the technology will proceed without any of the federal checks and balances we rely on to assure that medical research and practice are carried out with due regard for the safety and other interests of subjects and patients; such checks and balances include IRB review and approval, monitoring by the FDA of the sponsor and laboratories, and other

43. *See* Robert L. Stenger, *The Law and Assisted Reproduction in the United Kingdom and United States*, 9 J.L. & HEALTH 135 (1994-1995); *see also* Dresser, *supra* note 38.

practices common to most clinical trials.

President Obama's executive order of March 9, 2009,[44] "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," has taken a small step towards changing this balance. This order lifted the restrictions previously imposed by President Bush's 2007 order,[45] which had limited federally funded stem cell research to a set of lines created before August 2001. At the time of this writing, the NIH has drafted guidelines to implement President Obama's new policy,[46] setting forth "the conditions and informed consent procedures that would have been required during the derivation of human embryonic stem cells for research using these cells to be funded by the NIH."[47] These steps may be signs of increased federal involvement in stem cell research for both funding and regulatory purposes. However, the extent of this new federal involvement remains unclear. Given the continuing force of the Dickey-Wicker Amendment and the history of federal Pontius Pilate maneuvering regarding reproductive biology, a break from the past is by no means assured.

44. Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 9, 2009).

45. Exec. Order No. 13,435, 72 Fed. Reg. 34,591 (June 22, 2007).

46. Draft National Institute of Health Guidelines for Human Stem Cell Research Notice, 74 Fed. Reg. 18,578 (proposed Apr. 23, 2009).

47. *Id.* at 18,578.

Cloning and Stem Cell Debates in the Context of Genetic Determinism

Jane Maienschein*

When I studied introductory biology at the newly-coeducated Yale in the early 1970s, we didn't hear anything about stem cells. For that matter, we heard relatively little about embryos and development and much more about genetics and cell biology. The impression given was that cells are complex, they divide and multiply, and together they make up organisms. What seemed to matter most, however, were the genes, the nucleus, and to some extent the ways that genes cause the cells to act. Led by cell biologist J.P. Trinkaus, our course placed more emphasis on the interactions of cells than most courses of the time, but cell-cell interaction was not the central theme.

In biology generally, and certainly in the public mind, the "central dogma" of genetics had already taken hold and has only gained strength since. The message was that understanding biology must start with DNA, RNA, and their actions in producing proteins. Genes direct cells to develop, differentiate, and divide. Understanding development must start with the first cell, the egg cell, as it undergoes meiosis and casts off half its chromosomes in preparation for the fertilization process. Each cell division brings expression of different genes, and expression of these genes causes all the organic processes. And so it goes. Genes are inherited and they drive development; what follows is caused by heredity, or the doctrine of genetic determinism.

Or so it has seemed since DNA and genetics assumed a core place in biology in the 1960s and 1970s. What had been called embryology, or the study of embryos, became known instead as developmental biology and developmental genetics. The older emphasis on morphogenesis, differentiation, and cellular changes took a back seat to presumptions of genetic determinism as the cause of those developmental processes. My contention is that this emphasis on genetic determinism has reinforced a popular misconception that what matters about the life of an individual organism, including its form and function, is laid out fully in all relevant respects with fertilization, at the time that the full complement of chromosomes comes together from the two parents. This mistake is serious, since development actually occurs gradually, depends from the beginning on the

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environmental context and on cell-cell interaction to guide and inform the process, and is an epigenetic process that unfolds over time as the complex system develops.

To help address problematic genetic determinist views and to understand why they are problematic, this Article provides an historical look at the evolution of ideas of development. Rather than progressing through a recitation of chronology, however, the approach focuses on several clusters of contributions. Part I examines cloning and demonstrates what was meant by cloning, why the research developed, and with what results. Then came excitement about cloning combined with hopes for stem cell research for producing therapies—all in the context of genetic determinism. In Part II, I turn to issues of underlying assumptions and how they affect our understanding of life. In particular, genetic determinism and the assumption that development and differentiation occur in only one irreversible direction have caused problems. Part III looks in more detail at stem cell research as an alternative to genetic determinism and brings us to the nature of developmental science and who should count as an expert in this field. Finally, I present my conclusions.

I. EARLY CLONING RESEARCH

My first embryology course in graduate school was at Indiana University with Robert Briggs. Working with Thomas King in the early 1950s, Briggs had carried out the first successful cloning by nuclear transfer, which he performed using frogs.[1] King and Briggs transferred the nucleus from very early embryo stages of one species into the egg of another species and observed that the resulting frog was more like the donor than the host.

Researchers, especially John Gurdon, carried this nuclear transplantation technique further, even using cells from later stage embryos. Gurdon's frogs appeared on magazine covers, a large dark colored female and the small albino males, suggesting that the nucleus of the donor prevails at least in these visible respects over the influence of the host egg.[2] Gurdon had success with nuclei from somewhat later stages, reporting that about 30% of the nuclei transferred from blastula stages produced tadpoles, while 6% of nuclei taken from hatched tadpoles and only 3% from the even later stage of swimming tadpoles could produce successful clones that themselves developed to the tadpole stage.[3] This may seem like a small percentage, but note that Briggs and King had not had success with any later stage nuclei and had concluded that cloning is difficult and

1. Robert Briggs & Thomas J. King, *Transplantation of Living Nuclei from Blastula Cells into Enucleated Frogs' Eggs*, 38 PROC. NAT'L ACAD. SCI. 455 (1952).

2. *See, e.g.*, Anne McLaren, *Cloning: Pathways to a Pluripotent Future*, 288 SCIENCE 1775 (2000).

3. *Id.* at 1776.

that cloning from the late stages was not possible.[4] By the 1960s, "cloning" in this sense, by nuclear transfer, was a well-established research technique, allowing transfer of a nucleus from one individual to another in order to test the relative contributions of donor and host, and in order to assess the ability of the experimental system to respond to changing conditions.

As I began to do research with Briggs, he talked about this research into cloning. Why, he asked, was there so little public interest in the possibilities for cloning, perhaps even for reproductive reasons? He pointed to old magazines that showed a brief public attention to the experimentally produced hybrid frogs, but noted that publicity had declined quickly. Briggs felt that any cloning for reproductive reasons would surely raise ethical questions about what sorts of things scientists ought to do. He did not dismiss the possibility that nuclear transfer might be possible with human eggs, since he did not make the assumption as many researchers did that mammals (including humans) were too complex for nuclear transfer to be successful. Nor did he assume that any frog resulting from nuclear transfer would be like the donor nucleus rather than like the host embryo, since he was not a nuclear (or genetic) determinist. Instead he taught that developing embryos were highly responsive to their environments and that we knew little about the details of development. He was an embryologist who understood the complexities of the embryo and its ability to respond and adapt to changing environmental conditions. Briggs understood that, in science generally, we should expect the unexpected and keep exploring the range of what is possible; we must retain open minds about what science can achieve.

Briggs also noted that he and King had not been the first to imagine animal cloning through nuclear transfer. Embryologist Hans Spemann had raised the idea in 1938 in his Silliman Lectures presented at Yale. He had suggested a "fantastical" experiment[5] that he did not think should be terribly technically difficult. Spemann was thinking of frogs, which have large eggs that are plentiful and easy to work with. Already Spemann could transplant parts of different embryos and watch the resulting hybrid grow. Therefore, why not carry the transplantation one step further and transplant not just limbs and eye sockets but also a nucleus? He imagined that it would be possible to take a nucleus from one egg or embryo and transfer it to another that had had its embryo removed. Spemann never carried out his proposed experiment, but Briggs, King, and Gurdon did.

James Watson and colleagues may have had a typical geneticist's skepticism about the significance of animal cloning in their 1983 textbook, *Recombinant DNA: A Short Course*. Describing nuclear transfer in animals such as frogs in early developmental stages, they wrote, "In the immediate future there is little

4. *Id. See generally* J.B. Gurdon & Alan Colman, *The Future of Cloning*, 402 NATURE 743 (1999) (reflecting on early cloning research).

5. HANS SPEMANN, EMBRYONIC DEVELOPMENT AND INDUCTION 211 (1938).

likelihood of nuclear transplantation being attempted with any other mammalian species." They also noted, "If the efficiency and reproducibility can be improved, the method may, however, find a place in animal breeding. In theory it could be attempted with human eggs and embryonic cells, but for what reason? There is no practical application."[6]

No practical application for cloning? At the time, that conclusion could well have seemed sensible to geneticists not particularly interested in development or in frogs. Yet embryologists surely thought otherwise, since there was much interest in tools that could help us understand the developmental stages and the processes of morphogenesis and differentiation that take place gradually over time. Cloning in the sense of embryonic nuclear transfer, in fact, has proven itself useful as one such tool, and 1997 brought cloning to the public's attention.

In that year, Ian Wilmut and his team announced that they had cloned Dolly the sheep using nuclear transfer. This was the same basic technique that Briggs and King had pioneered, except that Wilmut and his team used adult somatic cells for the donor nuclei instead of nuclei from early developmental stages. Wilmut did not start with Briggs's and King's assumption that later stage nuclei would be too far differentiated and therefore a mismatch for the egg.[7] In fact, the many biologists who had made that standard assumption were shocked that Wilmut's laboratory's technique worked. Princeton Professor of Microbiology Lee Silver commented to *New York Times* reporter Gina Kolata that he had just completed a book claiming that such somatic cell nuclear transfer was impossible. As Gina Kolata reported, "'It's unbelievable,'" Dr. Silver said. "'It basically means that there are no limits. It means all of science fiction is true. They said it could never be done and now here it is, done before the year 2000.'"[8] Obviously, he was forced to revise the book that he had just been ready to send to press.[9]

Wilmut's group showed that cloning was indeed possible with adult mammals. Additionally, they showed that cloning had a practical application, namely in agriculture. Why not try to duplicate a cow that produces especially large quantities of milk? Why not replicate the cattle with the best beef, the fastest thoroughbreds, or the best-laying chickens? Agriculture had many uses for

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6. JAMES D. WATSON, JOHN TOOZE & DAVID T. JURTZ, RECOMBINANT DNA: A SHORT COURSE 207-08 (1983).

7. For discussion of these discoveries, see IAN WILMUT, KEITH CAMPBELL & COLIN TUDGE, THE SECOND CREATION: DOLLY AND THE AGE OF BIOLOGICAL CONTROL (2000). Ian Wilmut later explained that his colleague Keith Campbell was the leader on the project and that others in the team also contributed in important ways.

8. Gina Kolata, *Scientist Reports First Cloning Ever of Adult Mammal*, N.Y. TIMES, Feb. 23, 1997, at A1.

9. *See* LEE M. SILVER, REMAKING EDEN: CLONING AND BEYOND IN A BRAVE NEW WORLD (1997); Kolata, *supra* note 8.

somatic cell nuclear transfer. Some also saw the potential for the cloning of endangered species, at least for those where natural habitat still existed to allow benefit from a breeding program.

Of course, cloning adult humans is another matter. There was a strong public reaction against the idea of genetic copying or the prospects for what Gina Kolata imagined and many others echoed as a "time-delayed twin."[10] Few were troubled by the ethics of cloning sheep or cows, and some found the idea of cloning a favorite pet appealing. It was the prospect of human or other mammalian reproductive cloning that led to widespread debate all across the globe. Despite some initial curiosity and some rogue interests in individuals imagining cloning themselves, a strong consensus emerged by the end of 1997 among scientists that there was little reason for cloning humans for reproductive reasons.[11] Too many risks, too many unknowns, and too few justifications were already leading to a dominant view that this was one area of science that we should not carry out. We should not want to, nor need to clone human beings.

This conclusion, reinforced by all the well-funded bioethics discussions of the previous decade about the Human Genome Project, was that cloning involved genetic duplication, that genetics defined an individual's life, and that therefore a genetic duplication of persons would be morally and pragmatically unacceptable. Some felt that legislation prohibiting human reproductive cloning was warranted or perhaps that the 1974 National Research Act governing human subjects research already prohibited such experimentation.[12] Some hoped that the moral force of public opinion against cloning would prevail. With no compelling interests in human cloning, it seemed in 1997 that it was just a matter of working out details for prohibiting human cloning, ideally internationally.

This turned out to be not so easy, in large part because of the successes of stem cell research. We need to look at that work that began in 1998, when we learned about human embryonic stem cell research for the first time through the

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10. Kolata, *supra* note 8.

11. *See, e.g.*, NAT'L BIOETHICS ADVISORY COMM'N, CLONING HUMAN BEINGS (1997), *available at* http://bioethics.georgetown.edu/nbac/pubs/cloning1/cloning.pdf ("It seems clear to all of us . . . that any attempt to clone human beings . . . is unacceptably dangerous to the fetus and, therefore, morally unacceptable."); Andy Coghlan, *Cloning Report Leaves Loophole*, NEW SCIENTIST, June 14, 1997, at 77 (summarizing the conclusions of the National Bioethics Advisory Commission and noting the panel agreed that human cloning presented "unacceptable risks"); CNN Interactive, Scientist: Human Cloning 'Need Not Happen,' http://www.cnn.com/TECH/9703/12/cloning.news/index.html (last visited Apr. 21, 2009) (quoting Ian Wilmut saying in 1997 that human cloning "need not happen, and I hope it will not").

12. National Research Act, Pub. L. No. 93-348, § 201, 88 Stat. 348 (1974) (codified as amended in scattered sections of 42 U.S.C.) (establishing the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which later promulgated regulations for human subjects research (codified at 45 C.F.R. § 46 (2009))).

work of James Thomson and John Gearhart. Research had been underway for decades on mice, but the public had generally remained ignorant about stem cells. Thomson and Gearhart showed that the research on mice could now be extended to humans, and thus, they raised the possibility that stem cell lines might prove of therapeutic use,[13] even if not for purposes of reproducing "copies" of the cloned donor animal.

Thomson's work on human embryonic stem cells and Gearhart's work on human embryonic germ cells was announced against the background of heated discussions about cloning. Immediately and repeatedly, television and print news coverage combined the two. What did stem cell research mean for cloning, and what did research cloning mean for stem cell applications? After all, both are about embryos. The two lines of research were, naturally enough, conflated in the public mind. Those who had decided for whatever reasons that they hated the very idea of cloning immediately also hated stem cell research. Those intrigued by the scientific possibilities for cloning saw even greater prospects in combining the two. The neologism "therapeutic cloning" was created to describe cloning-for-research-purposes-only in order to separate it from "reproductive cloning," which would aim to produce babies. With so-called therapeutic cloning came the hope that the public imagination could be captured by the "therapeutic" opportunities rather than by the lingering negative of imagined duplicated humans.[14] Developmental biologists never lost sight of the research value in cloning, but they did lose control over the use of the technical term. The geneticist Lee Silver, for example, reported that a television producer had told him in 1998: "'Dr. Silver, you are not aware of what cloning can accomplish. Clones are not what you think they are.'"[15]

Stem cell research may have great potential application. Yet it has also led people to fall back on assumptions of genetic determinism and cloning. Geneticists have thought in terms of hereditary determinism, whereas stem cell researchers and developmental biologists have worked from assumptions of developmental plasticity, or the idea that it is the process of development in the context of changing environments that shapes the resulting organism along with the original inherited information. This idea of developmental plasticity is critical for stem cell research, which involves being able to direct undifferentiated stem cells to become different kinds of cells, depending on the environment of their

13. *See, e.g.*, John Gearhart, *New Potential for Human Embryonic Stem Cells*, 282 SCIENCE 1061 (1998); Michael J. Shamblott et al., *Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells*, 95 PROC. NAT'L ACAD. SCI. 13,726 (1998); James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145 (1998).

14. *See, e.g.*, David Magnus & Mildred K. Cho, *Issues in Oocyte Donation for Stem Cell Research*, 308 SCIENCE 1747, 1747-48 (2005).

15. Lee M. Silver, *What Are Clones? They're Not What You Think They Are*, 412 NATURE 21, 21 (2001).

culture medium. Yet assumptions of genetic determinism had come so overwhelmingly to dominate biology, and public impressions of life, that even fundamental work in areas of what had earlier been called embryology, such as the work by Briggs, King, and Spemann, was largely ignored.

In fact, those working in the embryological tradition had always realized that embryos retained a great deal of developmental plasticity and that they can respond and "regulate" within their changing environmental conditions. These researchers had continued to ask fundamental questions about differentiation and morphogenesis. They also recognized the special properties of stem cells to produce "immortal" undifferentiated cell lines while also being able to become differentiated under the right conditions. This is the idea of pluripotent stem cells: that under some conditions in the laboratory dish they can self-replicate forever (or so it is assumed), and with different culture media they can be made to become specific different kinds of differentiated cells (and have plural potential).

While some of these embryological scientists continued with their developmental studies, by the 1970s many researchers had followed the lure of genetics and molecular biology and set aside the complex system of cellular interactions that make up embryology. The Human Genome Project had so tipped the public perception, and some might argue even the actual practice, of biology that geneticists seemed to be able to serve as the experts for all matters of living organisms. Reporters turned to the familiar geneticists like Nobel Prize winner James Watson or familiar bioethicists, who had been enticed by the NIH's Ethical, Legal, and Social Implications (ELSI) genomics program to focus on genetics, as the appropriate "talking head" experts to help interpret stem cell science.[16] In fact, however, many of those researchers knew far less about the details of early development than developmental biologists would have, and their lack of expertise sometimes led to misinformation and confusion. Naturally enough, when scientists seemed to be contradicting each other or even correcting themselves, the appearance of professional confusion led to public annoyance and distrust. Why should the public, members of Congress, or reporters trust scientists who could not agree? It has taken some time for developmental biologists to emerge as legitimate authorities and experts in developmental biology and to help interpret the complexities of the developing organic systems.

To understand this particular situation more clearly, and also to look forward wisely, it will help to understand a bit more history. In particular, we need to appreciate the impact of underlying assumptions both in the scientific research and among the public, and why these assumptions matter. It matters greatly that genetic determinism came to dominate biology as well as the public

16. For example, Gina Kolata, in first breaking the cloning story for the *New York Times*, turned to geneticist and molecular biologist Lee Silver rather than a developmental biologist to explain the events. *See* Kolata, *supra* note 8.

perception of life. And it matters greatly that with genetic determinism has come an assumption that development is a matter of progressive differentiation caused by genes and expressed in the proper genetically-regulated sequence.

II. FUNDAMENTAL ASSUMPTIONS: GENETIC DETERMINISM AND UNIDIRECTIONAL DIFFERENTIATION

Where direct knowledge is impossible, biologists necessarily start working from assumptions. It is important to articulate and understand the impact of those assumptions, insofar as that is possible. Sometimes the assumptions become so widespread and well-established that it is difficult to get outside what Thomas Kuhn called the basic working assumptions of a paradigm.[17] Yet it is valuable to try. This section examines genetic determinism and unidirectional differentiation, two such assumptions in stem cell research. This section also discusses the difference between genetic determinism, the approach that primarily emphasizes the role of genes in development, and epigenesis which emphasizes the ways that cells may develop in response to contextual factors independent of inherited genes.

Since the early twentieth century, it has become commonplace to assume that each individual organism begins with inherited genes, located in the nucleus and organized along chromosomes. The genes, it seems, carry the information, or code, for the resulting characteristics of the organism. Development follows, with the cells in each developmental stage expressing (or becoming differentiated according to the instructions of) the appropriate piece of information programmed in the genetic code. The dominant assumptions of twentieth-century biology, therefore, included genetic determinism and the idea that differentiation occurs in one direction only, following the genetic program.

In the early twentieth century, hereditarians who held that characters are determined by their heredity (through genetics) led to an enthusiasm for eugenics as an effective approach to solving the perceived public health problem of a contaminated gene pool. Fortunately it became clear that we really knew little about inheritance, and the ill-advised eugenics programs mostly declined.[18] By mid-century, however, James Watson and Francis Crick's discovery of DNA structure quickly made it clear that "it has not escaped our notice that the specific pairing" of the nucleotides that make up DNA "immediately suggests a possible copying mechanism for the genetic material."[19] Heredity drives development, it seemed, and "defective" genes could be a new target for elimination, which many

17. THOMAS S. KUHN, THE STRUCTURE OF SCIENTIFIC REVOLUTIONS 23 (1962).

18. For an excellent overview, see DIANE B. PAUL, CONTROLLING HUMAN HEREDITY: 1865 TO THE PRESENT (1995).

19. J.D. Watson & F.H.C. Crick, *Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737, 737 (1953).

critics considered a new form of eugenics.[20]

With these assumptions in place, genetics became the backbone for teaching biology. The traditional problems of embryology, differentiation, and morphogenesis largely gave way to primacy for problems of molecules, genes, and cell biology. Of course, some researchers continued their studies of developmental patterns, including studies of stem cells: it has remained a core goal of biology to understand how, once we have particular genes, they are actually expressed. Most public attention remains focused on news about genetic correlations with diseases or hopes for genetically-based personalized medicine.

Molecular and cell biology programs are widely recognized as having proliferated in academic institutions, but they often require little understanding of the processes by which cells differentiate over time or of relationships among cells, organisms, and species. The implication of this investment is that if only we knew the human genome sequence, then we could solve medical problems. The Human Genome Project was certainly justified, given the availability of techniques for studying genetics and then genomics. But the single-minded focus on genetic determinism has had consequences.

The second fundamental assumption—the inevitability of unidirectional differentiation—is reinforced by the assumption of genetic determinism. When we watch a fertilized egg develop through each successive stage, it is natural to see it as becoming more differentiated. It is not unreasonable to see the process of increasing differentiation as determined by some internal driver (the genes are today's choice, even though earlier generations tried invoking internal gradients and other chemical factors). And it is also reasonable to see the process as unidirectional. Once cells and body parts are appropriately differentiated, the natural assumption is that they stay differentiated. That is what we seem to see under normal conditions, and it is reasonable to assume that that is the way differentiation works. Why would differentiation be other than in the progressive and forward direction of increasing cell specialization and organismal complexity?

Yet in the absence of all the data we have today, the late nineteenth and early twentieth century biologists experienced great disagreement about this point. Some researchers such as August Weismann and Wilhelm Roux were strong hereditary determinists, but theirs was the minority position.[21] Weismann and Roux believed that the individual inherited its germ plasm from both parents, and the hypothetical units (called determinants by Weismann) that made up the nuclear chromosomes were then divided into the different cells during cell division. They hypothesized that the determinants were actually parceled out,

20. *See, e.g.*, THE CODE OF CODES: SCIENTIFIC AND SOCIAL ISSUES IN THE HUMAN GENOME PROJECT (Daniel J. Kevles & Leroy Hood eds., 1992); ROBERT COOK-DEEGAN, THE GENE WARS: SCIENCE, POLITICS AND THE HUMAN GENOME (1994).

21. JANE MAIENSCHEIN, WHOSE VIEW OF LIFE 72-74 (2003).

yielding a mosaic of different cells. Even when it became clear that the complete chromosomal complement remained whole in each cell, however, they just invoked a selective expression of different determinants in each cell. Their overarching view was, in effect, consistent with genetic theory today.

But others—indeed the vast majority of embryologists and histologists (as cell biologists were called then)—complained that Weismann and Roux provided no explanation of development at all.[22] These researchers saw complexities, responses to changing environmental conditions, and interactions among cells and parts. Development was not predetermined by inheritance, they concluded, but was a gradual response of the integrated and interactive whole organism to its changing environment. As Edmund Beecher Wilson acknowledged in the title of his classic, *The Cell in Development and Inheritance,* an organism needs both that which is inherited—the germ cells with their nuclear chromosomes—and the capacity to respond to the particular conditions.[23] For these biologists, development was an epigenetic process and not a matter of preformationism or even the sort of internal predeterminism that Weismann and Roux offered. They explicitly and repeatedly rejected such a hereditarian account as hypothetical, not grounded in evidence, and as too simplistic to explain the complexities of development and differentiation.[24]

This has been a core debate about the nature of life reaching back to Aristotle. William Morton Wheeler summarized debates about Weismann's ideas in 1899 by suggesting that there are two different kinds of thinkers. Some see change and process, while others see stability. Heraclitus, Aristotle, physiology, and epigenesis characterize one way of looking at the world; Parmenides, Plato, morphology, and preformationism characterize the other. These are, Wheeler felt, stable and persistent classes, and yet the nature and details of their differences have changed over time. Wheeler argued that by the end of the nineteenth century neither a strict preformationist nor a strict epigeneticist who ignored new evidence and new reasoning could succeed. In the end, it is not to philosophy but to science that we must look to resolve the relative contributions of hereditary pre-determinism and regulatory development, for "[b]oth tendencies will find their correctives in investigation."[25]

Today, we are in a similar situation except that the preformism of genetic determinism has overbalanced our understanding of complex developmental

22. For a summary, see EDMUND BEECHER WILSON, THE CELL IN DEVELOPMENT AND INHERITANCE 303-31 (1st ed. 1896).

23. EDMUND BEECHER WILSON, THE CELL IN DEVELOPMENT AND INHERITANCE (2d ed. 1900). This volume was later retitled. THE CELL IN HEREDITY AND DEVELOPMENT (3d ed. 1925).

24. For discussion, see JANE MAIENSCHEIN, TRANSFORMING TRADITIONS IN AMERICAN BIOLOGY, 1890-1915 (1991).

25. William Morton Wheeler, *Caspar Friedrich Wolff and the Theoria Generationis, in* DEFINING BIOLOGY: LECTURES FROM THE 1890S, at 195, 216 (Jane Maienschein ed., 1986).

processes. We have forgotten Wheeler's plea for a balanced view. We have forgetten that when Hans Driesch shook apart the first two cells of the sea urchin egg, they did not result in two half embryos, as Roux had predicted, but instead in two smaller larval urchins.[26] We have forgotten the extensive work that Thomas Hunt Morgan did on regeneration of a large number of different animals, showing the extent of developmental plasticity.[27] We have even forgotten the work of John Tyler Bonner on morphogenesis and the relations of parts in the developing interacting organism.[28] These studies show the capacity of the individual to regulate its development in the context of environmental change, even with experimental assaults like shaking apart the first two cells or chopping up the embryo into bits of organism like earthworms to watch them regenerate into two new worms.

Biologists have also forgotten the early work on stem cells and their developmental plasticity. It is worth reminding ourselves of this work, if only to help illuminate the power of the underlying assumptions. If biologists had had these earlier studies more clearly in mind, or if reporters had called on experts who knew this developmental research rather than appealing mainly to geneticists, the public might not have been so shocked by the cloning and stem cell discoveries of the late 1990s. They might even have been able to forestall the preformationist conclusions that fit so tidily with ultra-conservative religious assumption that life begins absolutely at the moment of fertilization or "conception"—the moment of genetic union—even though the now-fertilized egg remains completely undifferentiated and unformed.[29]

This is the key point: the biology that we have actively and visibly promoted (and with which the public is most familiar) is a biology that relies heavily on predeterminism. Until the public appearance of human stem cell lines, we did not see the biology of epigenetic development or the sort of moderated balance that Wheeler called for over a century ago. If some scientists claim that each organism begins with inheritance of genes, with development simply expressing the genetically preprogrammed sequence of steps, it is difficult to explain the complexities of developmental processes to those in the public who insist as a matter of faith that "life begins at conception." It is ironic that those who most vehemently insist that they are "pro-life" in all its forms are those adopting a biological determinism and denying the "free will" of developmental plasticity of

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26. Hans Driesch, *Entwicklungsmechanische Studien. I. Der Werth der beiden ersten Furchungszellen in der Echinodermentwicklung. Experimentelle Erzeugen von Theil- und Doppelbildung*, 53 ZEITSCHRIFT FÜR WISSENSCHAFTLICHE ZOOLOGIE 160-78 (1892), *translated in* FOUNDATIONS OF EXPERIMENTAL EMBRYOLOGY 38-50 (Benjamin Willier & Jane M. Oppenheimer eds., 1964).

27. *See* THOMAS HUNT MORGAN, REGENERATION (1901).

28. *See* JOHN TYLER BONNER, MORPHOGENESIS (1952).

29. MAIENSCHEIN, *supra* note 21, at 3.

the individual. This view of genetically determined life is probably not, in fact, what they have in mind. We must make this point clear in order to gain wise traction on the problem of competing entrenched views. To understand the alternatives, let us look briefly at the history of stem cell science.

III. STEM CELL HISTORY: AN EPIGENETIC ALTERNATIVE

Like cloning, stem cell research did not suddenly begin out of nothing in 1998. In fact, also like the term "cloning," the term "stem cell" was first used in the late nineteenth century. Both concepts began in botany where cloning meant production of identical individual plants. Stem cells referred to undifferentiated cells that retained their undifferentiated state. Edmund Beecher Wilson and his friend and collaborator William Sedgwick were the first ones to use the term in the late 1800s.[30] They did not, of course, know about the range of different types of stem cells that we have identified since, nor did they culture stem cell lines or look at mammalian cells. Yet they identified the original concept, and other research in embryology and cytology later confirmed that some cells retain flexibility and the ability to respond to environmental conditions.

Ross Granville Harrison, working first at Johns Hopkins and then at Yale, carried out the first successful tissue culture experiment, which was also the first stem cell experiment.[31] He did not label the neuroblasts (embryonic cells that give rise to neural cells) that he cultured "stem cells," nor did he develop a stem cell line or any of the other key elements we use today to define the cells. In retrospect, however, this was the first stem cell experiment, using cells that we recognize as neural stem cells and carrying out the first ever cell and tissue culture.

Harrison asked a core embryological question: how does a cell differentiate? In particular, he wanted to shed light on the heated contemporary debate about the nervous system. The question was, how do individual cells "know" where to go? Do they follow predetermined paths that are laid down in the developing embryo? Or, in contrast to this preformationist view, could the process be epigenetic? That is, might the cells develop independently, each following its own internal direction to a point but taking its cues from the surrounding environment? In this case, was it the interactions of the whole organism that influence how each cell develops? Preformation or epigenesis: this was the old question in a new form.

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30. *See, e.g.*, 16 OXFORD ENGLISH DICTIONARY 627 (2d ed. 1989) (defining "stem" and noting early references to the term "stem cell," including an 1896 reference from E.B. Wilson that distinguishes stem cells from somatic cells) (quoting WILSON, *supra* note 22, at 111). For further discussion, see Jane Maienschein, *What's in a Name: Embryos, Clones, and Stem Cells*, 2 AM. J. BIOETHICS 12 (2002).

31. MAIENSCHEIN, *supra* note 24, at 261-89.

Harrison followed the same reasoning as Spemann, looking to discover the results of transplanting cells. Instead of transplanting such parts as limbs from one embryo to another, which is what researchers had done in the past, and instead of transplanting the nucleus as Spemann had suggested, Harrison proposed to go further. Why not actually explant the cells? Just take them out of the body altogether. Might it not be possible to take those cells known to give rise to the nerve fibers (the neuroblasts), remove them from their normal surroundings, place them into a culture medium, and see what they will do? If they behave more or less normally, this would suggest that they follow an epigenetic interaction with their environment as they grow under normal conditions, as in the experimental case. Harrison concluded that the nature of the processes was fundamentally the same and that more research was needed to discover the other factors involved. This experiment was not easy, and Harrison first had to develop a culture medium on which the cells could grow. Fortunately, he moved to Yale in 1907 and was temporarily housed near the bacteriologists. They taught him about aseptic conditions, and his technique improved dramatically.[32]

Harrison decided that he had obtained what he wanted from the experiment, namely another piece of evidence about the epigenetic nature of development. He did not pursue tissue culture further because he was interested in different questions that called for different methods. Yet others did take up the approach, notably Alexis Carrel at the Rockefeller University.[33] He and other tissue culture researchers set down the foundations for later stem cell research, establishing techniques for successful cell culture and demonstrating the considerable plasticity and ability to respond to surrounding conditions of many types of cells and tissues.

That was a foundation, but it was the work on hematopoeitic stem cells that started serious interest in human stem cells and their potential applications. Already in the eighteenth century, some adventurous experimenters had apparently carried out animal to human blood transfusions, though the earliest rumors are not well documented. In 1795, Philip Syng Physick reported having transfused blood from one human to another for the first time. This broke down any assumption that humans were entirely unique and instead showed a common physiology. In the twentieth century, blood transfusions became routine as researchers worked out ways to control immune responses, to recognize and match blood types, and to prevent clotting.[34] Yet despite this great advance,

32. *See* Ross Granville Harrison, *The Outgrowth of the Nerve Fiber as a Mode of Protoplasmic Movement*, 9 J. EXPERIMENTAL ZOOLOGY 787 (1910).

33. *See* CREATING A TRADITION OF BIOMEDICAL RESEARCH: CONTRIBUTIONS TO THE HISTORY OF THE ROCKEFELLER UNIVERSITY 135-50 (Darwin H. Stapleton ed., 2004).

34. For the well-known history of blood transfusion, see SUSAN E. LEDERER, FLESH AND BLOOD: ORGAN TRANSPLANTATION AND BLOOD TRANSFUSION IN TWENTIETH-CENTURY AMERICA

transferring blood from one person to another cannot solve all problems, and it always carries risks, including potential rejection or infection.

Discovery is sometimes stimulated by crisis. In France in the 1950s, a serious radiation accident produced a number of victims with various forms of leukemia, a blood disease.[35] It was already known that blood cells arose in the bone marrow, apparently from hematopoeitic stem cells. A flurry of research prompted by the French crisis led to discovery of the human leukocyte antigen that allowed the individual's body to distinguish between itself and other foreign cells and to initiate the body's effort to destroy the foreign invaders. How could medical science override the protective systems? By the 1960s, researchers conducted the first transplantation of bone marrow into a child with immunodeficiency disease, and the first marrow transplants on an unrelated patient occurred in 1973.[36]

While these human success stories were remarkable, the major study of stem cells and their possibilities remained focused on mice. Mice are relatively easy to study, available from supply houses in genetically controlled lineages, and enough like humans to be a better model system than fruit flies, frogs, or nematode worms. In the 1970s Leroy Stevens was already following up earlier studies of abnormal developmental results such as teratomas. What caused such disorganized masses of "monstrous" cells in the mouse, he asked? If we could understand the cause of teratogenesis, we might begin to understand the causes of cancers and also the causes of normal differentiation.[37] During the next decades, many more researchers in a number of different labs took up mouse embryology, including a focus on the patterns of differentiation of embryonic stem cells.

Until the 1990s, the potential human applications of knowledge derived from mouse studies remained unclear. Embryonic stem cells were fascinating precisely because their fates were unknown and because they, in theory, had the capacity to differentiate into any and every separate kind of cell (though not necessarily in any organized way, and therefore, they are not totipotent and cannot become the whole). Yet because of this, they also could produce a tangle of wildly differentiated cells. Teratomas were common, for example, yielding a mix of teeth, hair, and other differentiated cells all jumbled together. Therefore, simply transplanting embryonic stem cells might well have yielded a muddle of cells

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(2008); PBS, Red Gold: 1700-1919 Discovery and Exploration, http://www.pbs.org/wnet/redgold/history/timeline3.html (last visited Apr. 21, 2009).

35. MAIENSCHEIN, *supra* note 21, at 252.

36. *See, e.g.*, Cynthia M. Piccolo, Transplant Timeline – Bone Marrow Transplants, http://www.medhunters.com/articles/transplantTimelineBMT.html (last visited Apr. 21, 2009) (providing a history of bone marrow transplants).

37. *See* R. Lewis, *A Stem Cell Legacy: Leroy Stevens*, 14 SCIENTIST 19 (2000); *cf.* L.C. Stevens, *Teratogenesis and Spontaneous Parthenogenesis in Mice*, *in* THE DEVELOPMENTAL BIOLOGY OF REPRODUCTION 93 (Clement L. Markert & John Papaconstantinou eds., 1975).

rather than anything medically useful. Researchers were well aware of these limitations, and yet some persisted in developing embryonic stem cell lines in the hope that they would help us learn more about the nature of differentiation, and also because there was always the possibility that we could learn to engineer these cells to do what we wanted and to make them predictable.[38]

This drive to understand and control differentiation is a basic foundation of medicine and applied biology. It is not new. As historian Philip Pauly brilliantly showed, in the late 1890s Jacques Loeb was already promoting a "mechanistic conception of life."[39] Loeb produced parthenogenetic (asexual) sea urchins, eggs that divided and differentiated up to the pluteus larval stage. Loeb accidentally discovered that by changing the concentration of salt in the sea water, he could produce female sea urchins that did not need males to reproduce. The front pages of newspapers announced, "Science Nears the Secret of Life."[40] If fertilization was not even necessary, and eggs could develop on their own, then females could produce their own offspring.

That was in 1899. The assumption was that with proper knowledge and techniques, scientists could control and engineer life processes. Today, scientists including Robert Lanza of Advanced Cell Technology reflect the same thinking.[41] So do many of the scientists who led the advocacy march for funding for stem cell research in California and other states. If only we had money, they reasoned, we could take stem cell lines like those James Thomson produced in 1998, and we could get them to do what we want them to do. Then, since they would be differentiated according to our direction, we might assume that once a cell becomes a heart muscle (or brain or pancreas or whatever it is that we want) it will stay that sort of cell and function the way it is supposed to.

There is something exciting and high-minded about this view. In 1909, Loeb's success brought considerable excitement and heavy financial support from the Rockefeller Institute.[42] There was great hope for medical progress. And so we think today. But we should also be wiser now, over a century later. If we

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38. *See, e.g.*, M J. Evans & M.H. Kaufman, *Establishment in Culture of Pluripotential Cells from Mouse Embryos*, 292 NATURE 154 (1981); Gail R. Martin, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells*, 78 PROC. NAT'L ACAD. SCI. 7634 (1981).

39. PHILIP PAULY, CONTROLLING LIFE: JACQUES LOEB & THE ENGINEERING IDEAL IN BIOLOGY 130 (1987) (quoting PAUL DE KRUIF, THE SWEEPING WIND: A MEMOIR 42 (1962)); *id.* at 100. On this point, see Jane Maienschein, *Controlling Life: From Jacques Loeb to Regenerative Medicine*, J. HIST. BIOLOGY (forthcoming 2009).

40. *See* PAULY, supra note 39, at 218 n.31 (citing *Science Nears the Secret of Life*, CHI. SUNDAY TRIB., Nov. 19, 1899, at 33); *id.* at 100-02.

41. *See* Advanced Cell Technology, Fact Sheet, http://www.advancedcell.com/fact-sheet (last visited Apr. 21, 2009).

42. *See* PAULY, *supra* note 39, at 135-36.

are selecting cells precisely because they are pluripotent and capable of diverse differentiation, then assuming that we can cause them to differentiate exactly as they would normally involves assumptions more simplistic than those Ross Harrison made a century ago. Also, we are discovering with cloning and other related research that differentiation is not unidirectional. Indeed, some of the leading stem cell researchers talk freely about "resetting the developmental clock," "reprogramming," or "de-differentiating" cells.[43] Recently, several different laboratories have de-differentiated cells and reprogrammed them to act as if they were pluripotent stem cells.[44] If we can de-differentiate cells, then why do we assume that our engineering process will produce cell lines that, even once properly differentiated, will stay differentiated and continue to do what we want them to do?

Many questions remain, and they are wonderfully exciting questions that strike at the very heart of how development works. Researchers around the world are sharing some of their results (when not restricted by the intellectual property demands of private funding) and are benefiting from a major infusion of funding and attention to stem cell science as through the California Initiative funding.[45] What history shows us is that what we actually come to know and what we are able to do may be very different from what we expect. It may well turn out that pluripotent embryonic stem cell lines are useful for research now, but that what we really need are multipotent or unipotent precursor cells that are already partly differentiated. Perhaps these cells will be more likely to stay differentiated in the desired way once they are transplanted for use. We may come to appreciate the complexity of developmental responses to changing environmental conditions, tempering our genetic determinism with the gradual, epigenetic, development of differentiation and morphogenesis. Perhaps we can even learn that life is both more complex than simplistic genetic determinist views might have it, and more comprehensible and manageable than extreme epigenetic assumptions of complexity would demand. Just as Wheeler suggested over a century ago, wisdom may lie in seeking a middle ground, arriving at understanding not through philosophy and assumptions but through scientific exploration and evidence.[46]

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43. *See, e.g.*, Nicole Rusk, *Resetting the Clock*, 3 NATURE METHODS 72 (2006).

44. *See* Keisuke Okita, Tomoko Ichisaka & Shinya Yamanaka, *Generation of Germline-Competent Induced Pluripotent Stem Cells*, 448 NATURE 313 (2007); Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917 (2007).

45. *See, e.g.*, California Institute for Regenerative Medicine, About CIRM, http://www.cirm.ca.gov (last visited Apr. 21, 2009).

46. *See supra* note 25 and accompanying text.

CONCLUSION

We see that it was largely because of exuberance for genetic determinism that we were surprised by cloning and then by stem cell research. We might have predicted these developments if we had had a more robust sense of the range of developmental possibilities and plasticities, and ideally even a sense of the history—both the history of science and the history of the complex developing organism. Instead, cloning and later stem cell research have created fears and worries about genetic duplication of persons. This fear hinges on the highly problematic assumption that a person is nothing more than the expression of the genetic complement.

Furthermore, public discussions have been distorted by more than the abortion debates, the absence of scientific knowledge, and the appeal to genetics experts as definitive sources of understanding; public debate has also been distorted by the bioethics industry. Well-meaning academics have been strongly supported for almost two decades by the Human Genome Project's ELSI program at NIH to study the implications of the genome project.[47] These academics are the experts to whom reporters and commentators turned for an ethical view of cloning and stem cell research.[48] Few were familiar with the developmental biology involved, and since they had been focused on and trained in other, largely genetic or general medical issues, they made mistakes about the science. Others have been exemplary in their caution, but nonetheless fall back on analogies to genetics. This case raises questions about who the experts should be in highly contested public discussions of science.

Surely, developmental biologists are relevant experts on the science involved. It is entirely appropriate to ask Ian Wilmut, James Thomson, Irving Weissman, George Daley, or Evan Snyder, for example, to explain their research. It is entirely appropriate even to ask what they see as the implications or possible applications, for example. It is even reasonable to ask them for their personal interpretations of what is at issue ethically; however, then they are offering just that—one individual's personal opinion. Bioethicists can also have individual personal opinions as well as professional analyses. Poets or engineers or schoolchildren may also have personal opinions, and only some are experts with respect to any particular question. Historians of science may even have opinions, including informed and helpful opinions. They may all have opinions about what is at issue, about values, and about proposed social actions. It is entirely appropriate, and indeed even necessary, that members of society individually and society as a whole have input into decisions about social actions, even those relating to the funding and regulation of science.

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47. *See* National Human Genome Research Institute, ELSI Research Program, http://www.genome.gov/10001618 (last visited Apr. 21, 2009).

48. *See, e.g.*, COOK-DEEGAN, *supra* note 20.

What is not appropriate, however, is that social commentators *interpret* the science according to their own assumptions and values, and then present these interpretations as fact. Just as it is not appropriate for scientists to decide by themselves, on the basis of the science alone, what is moral or what ought to be legal, so it is not appropriate for citizens to decide by themselves, on the basis of their values alone, what scientific research is "moral," "good," or legally defensible.

In the heated and highly polarized political climate of the late twentieth and early twenty-first century, we have somehow allowed some particular groups to define the important questions what counts as scientific knowledge. In particular, the religiously-infused debates about abortion politics have been allowed to influence the discussion about embryo research far more than is warranted by the nature of the "expertise." Somehow, public debates about stem cell research have become debates about whether we want to save the pre-implantation embryos that these groups take as "persons" or whether we want to help save the lives and improve quality of lives for those suffering from degenerative diseases. These are the wrong questions, or at least they are not the only relevant and important questions. Let us start by asking about the empirical facts about developing embryos.[49]

In particular, scientists show that at first an embryo *in vitro* is really a bunch of undifferentiated cells in a dish.[50] It would be scientifically unsound to insist that the earliest stage fertilized egg is biologically as developed as the later-stage fetus with all its body parts intact, including the beginnings of a beating heart and sensory system. Neurobiologist and member of the President's Council on Bioethics Michael Gazzaniga put it beautifully:

> It is a truism that the blastocyst has the potential to be a human being. Yet at that stage of development it is simply a clump of cells. . . . An analogy might be what one sees when walking into a Home Depot. There are the parts and potential for at least 30 homes. But if there is a fire at Home Depot, the headline isn't 30 homes burn down. It's Home Depot burns down.[51]

Or as developmental biologist Lewis Wolpert has aptly explained, it is only with implantation and the stages after the blastocyst that biological differentiation starts to occur so that gastrulation (the point at which the germ layers first begin

49. *See, e.g.*, Jane Maienschein et al., *The Ethos and Ethics of Translational Research*, 8 AM. J. BIOETHICS 48-49 (2008) (noting the "rush to translation" from fundamental stem cell research to clinical applications, which may "undercut[] [scientists'] abilities to study other kinds of fundamental developmental processes" and paradoxically hamper the lab science necessary for building therapeutic applications).

50. *See* Glenn McGee & Arthur L. Caplan, *What's in the Dish?*, HASTINGS CENTER REP., Mar.-Apr. 1999, at 36.

51. *Metaphor of the Week*, 295 SCIENCE 1637 (2002) (quoting Michael Gazzaniga).

to form) is "truly 'the most important event of your life.'"[52] Embryos go through developmental stages, as biologists have documented clearly for a century and a half, and each of those stages has a different biological "meaning."

The earliest cell divisions are just that—divisions of material. It is as if we were cracking a glass window into a bunch of smaller pieces, but the whole hasn't grown any larger. It's now just a number of pieces rather than one unified part. Yes, these are still cells and they are "living" in some sense. But without any significant genetic action, and without any differentiation, they really do seem biologically to be "just" cells in a dish. To suggest that these are equivalent to a fully developed person is to devalue that person and the complex processes that have made him or her into the individualized self that results.

Cells divide and divide up to the eight cell stage, and as far as we can tell, in the earliest divisions there is no significant genetic action and no differentiation. This is why the eight cells are all totipotent, each capable of becoming an individual if separated from the rest of the cells. It is also why biologically we can remove one or two of the eight cells (which is sometimes done in fertility clinics for purposes of genetic testing) and the rest can still develop into a perfectly healthy baby.[53]

It is also why we might be able to take one or two or even up to seven cells of the eight-cell stage and take them off to be developed to the blastocyst stage and then harvested for stem cells. We would still have the one individual person we would have had, without any loss of genetic information. But now we have seven stem cell lines all genetically alike. Such an approach might address some ethical concerns, since the one cell still becomes one individual organism with a particular genetic makeup; but now there are also extra cell lines with the same genetic makeup as well. Why not try it?

Developmental biologists might well ask such questions. The public might well ask such questions. Why not try such experiments? Why have we allowed those who are essentially genetic determinists and who insist that all stages of life are equally important to dominate the social and political discussion; why do we defer to those who refuse even to discuss more nuanced possibilities to define the terms of the debate? Partly, I suspect, this is because of the nature of the arguments about cloning, which created a focus on issues of "personhood." And partly because of the history of bioethics as a field. Also, and perhaps most importantly, because too many biologists themselves have been seduced by

52. LEWIS WOLPERT, TRIUMPH OF THE EMBRYO 12 (1991).

53. There is some controversy about whether such preimplantation genetic diagnosis leads to problems or is a socially important tool. *See, e.g.*, RUTH SCHWARTZ COWAN, HEREDITY AND HOPE: THE CASE FOR GENETIC SCREENING (2008); Stéphane Viville, Deborah Pergament & Morris Fiddler, *Ethical Perspectives and Regulation of Preimplantation Genetic Diagnostic Practice*, *in* PREIMPLANTATION GENETIC DIAGNOSIS 227 (Joyce C. Harper, Joy D.A. Delhanty & Alan H. Handyside eds., 2001).

genetic determinist thinking. They find it difficult now really to understand and to adopt the more epigenetically balanced understanding of development and differentiation that the science demands and from which the social needs might well benefit.

If we are all experts in some ways on these questions, let us assume our mantel of expertise wisely and seek to understand the full range of questions and possible interpretations. Let us work hard to identify and also to question our assumptions about development and its meanings. As Wheeler urged in 1899, let us work toward wise and balanced interpretations that respect as wide a range of views as possible without giving in to extremism on any side.[54]

54. *See* Wheeler, *supra* note 25, at 216.

The Ethics of Embryonic Stem Cell Research and the Principle of "Nothing is Lost"

Gene Outka*

Hype tempts us all. It would be naive to exempt scientists from sometimes overstating the promise of their research. Early claims about what gene therapy would accomplish, for example, were arguably exaggerated and eroded public confidence. Yet claims about what stem cell research may accomplish belong in a class by themselves. The general public is now convinced that something momentous is occurring.[1] Both professional and popular publications register the excitement that scientists evidence. This research, it is routinely said, will not only expand significantly what we know about cellular life, but it will also bring dazzling clinical benefits. Those who suffer from Alzheimer's disease, Parkinson's disease, and others are regularly identified as eventual beneficiaries. Because these possibilities are now widely accepted as truly feasible, researchers secure vaster amounts of material support all the while.

Whether these claims too will prove exaggerated awaits research efforts that are still in their early stages.[2] In the case of embryonic stem cell research, consider this sobering report: "To date, no therapeutic applications of embryo-derived cells have been demonstrated, and only one preliminary human trial has been approved by the FDA (though it has yet to begin)."[3] Some scientists acknowledge with an honesty I admire that they are still years away from broadly

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1. For one early, engaging indication, see Gregg Easterbrook, *Medical Evolution*, NEW REPUBLIC, Mar. 1, 1999, at 18. For a comparative survey, see Matthew Weed, *Discourse on Embryo Science and Human Cloning in the United States and Great Britain: 1984-2002*, 33 J.L. MED. & ETHICS 802 (2005). For a broad survey of scientific, ethical, and religious issues, see THE STEM CELL CONTROVERSY: DEBATING THE ISSUES (Michael Ruse & Christopher Pynes eds., 2d ed. 2006).

2. Sharon Begley, *Reality Check on an Embryonic Debate*, NEWSWEEK, Dec. 3, 2007, at 52; Maureen L. Condic, *The Basics About Stem Cells*, FIRST THINGS, Jan. 2002, at 30.

3. Yuval Levin, *Biotech: What To Expect*, FIRST THINGS, Mar. 2009, at 17, 18.

applicable therapies. We long for such benefits, of course, and most of us sense a genuinely other-regarding motive at work among those who make claims about benefits. That is, the prospect such research affords for bringing concrete relief to numerous human sufferers motivates scientists to engage in it. We discern and respect this motive, although we do well to acknowledge that less altruistic considerations, such as a search for funding and profits, sometimes operate as well.

This Article takes general stock of moral judgments about *embryonic* stem cell research in particular and offers one specific resolution. It canvasses a spectrum of value judgments on sources, complicity, and "adult" stem cells.[4] It proposes to extend the principle of "nothing is lost" to current debates. This extension links historic discussions of the ethics of direct killing with unprecedented possibilities that *in vitro* fertilization procedures yield. The creation of embryos solely for research purposes should be resisted, yet research on "excess" embryos is permissible by virtue of an appeal to the "nothing is lost" principle.

The ethical controversies surrounding this research press chiefly in two directions: 1) the other-regarding motive to benefit human sufferers, and 2) the moral status of the embryo. Even as we praise the motive, we confront complicating moral questions about according this motive utter priority. Should research that accents benefits to human sufferers trump all other considerations as it seeks to secure these benefits? What of embryos themselves? Should we, without a second thought, reduce their value *totally* to their importance for relieving the suffering of *third* parties? May a readiness to do anything that we please with and to embryos be acceptably other-regarding after all? What other moral considerations count and how much should they count? I approach these questions with lenses through which I see a more encompassing diagnosis of ourselves. Two basic generalizations about us that derive from this diagnosis influence my reflections in what follows.

First, we are *morally capable* creatures, *accountable* beings. We should assume responsibility for what we are doing, and we go wrong when we seek to deny our agency. Second, we are creatures who can *exalt ourselves inordinately*, in ways that flout God and manipulate others. This condition is called sin and moral evil in many religious communities. To be tempted to usurp and to do injustice is endemic to human life as we know it. In my own identity as an

4. I mention but do not focus here on alternative sources of stem cells: adult, umbilical cord, placental, amniotic, and others. *See infra* note 23. To restrict attention to the embryonic is justified because this source raises distinctive moral considerations and because many still hold that – except for the practical difficulties created by ethical controversies – it is the best for research purposes among the alternatives. Further, most of the moral considerations I identify require me to distinguish between embryonic stem cells on the one hand, and adult and other alternative-source stem cells on the other.

Augustinian Christian, I take it that we are continually in danger and that everything is corruptible.[5] If this is right, we should expect that embryonic stem cell research is itself not immune to pressures that may usurp and do injustice. In short, we are contending in the case of such research with novel opportunities and challenges, and with permanent capabilities and dangers. In what follows I characterize moral controversies that surround embryonic stem cell research in Part I; I assess them for myself in Part II; and I offer concluding remarks in closing.

I. RECURRING ETHICAL CONTROVERSIES

I focus on three points where value judgments collide: the *status* of the fetus and of the embryo; the question of *complicity*, where research depends on someone destroying a fetus or an embryo; and the *alternative* of concentrating on stem cells found in adults. Particular evaluations of these three issues tend to cohere internally. I review a spectrum of rival value judgments that pertain to each point.[6]

A. Views on the Right

By views on the right, I refer mostly to Richard M. Doerflinger, who defends in lucid prose Vatican instruction on human procreation. Yet we should not suppose that only Roman Catholics reach the judgments I describe; many

5. *See* Gene Outka, *Augustinianism and Common Morality*, *in* PROSPECTS FOR A COMMON MORALITY 114 (Gene Outka & John P. Reeder, Jr. eds., 1993).

6. These judgments recur in various religious traditions; they are by no means confined to Christianity. Because many Jewish thinkers take the moral standing of the early fetus as subordinate to the mother (in cases of pregnancy following rape, for example, her pain comes first), and because they nevertheless want to promote life and reduce suffering, they may laud stem cell research generally and embryonic stem cell research specifically. *See* Ellen N. Dorff, *Testimony of Rabbi Ellen N. Dorff, Ph.D.*, *in* 3 NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, at C-1 (2000), *available at* http://bioethics.georgetown.edu/nbac/stemcell3.pdf; Moshe Dovid Tendler, *Testimony of Rabbi Moshe Dovid Tendler, Ph.D.*, *in* NAT'L BIOETHICS ADVISORY COMM'N, *supra*, at H-1; Laurie Zoloth, *Testimony of Laurie Zoloth, Ph.D.*, *in* NAT'L BIOETHICS ADVISORY COMM'N, *supra*, at J-1. Less reflection on stem cell research appears in the Islamic tradition to date. *But see* Abdulaziz Sachedina, *Testimony of Abdulaziz Sachedina, Ph.D.*, *in* NAT'L BIOETHICS ADVISORY COMM'N, *supra*, at G-1. Views on abortion prove complex, moreover; both conservative and more permissive judgments appear. For one instructive survey, see Marion Holmes Katz, *The Problem of Abortion in Classical Sunni* Fiqh, *in* ISLAMIC ETHICS OF LIFE: ABORTION, WAR, AND EUTHANASIA 25 (Jonathan Brockopp ed., 2003). *See also* Donna Lee Bowen, *Contemporary Muslim Ethics of Abortion*, *in* ISLAMIC ETHICS OF LIFE: ABORTION, WAR, AND EUTHANASIA, *supra*, at 51; Vardit Rispler-Chaim, *The Right Not To Be Born: Abortion of the Disadvantaged Fetus in Contemporary Fatwas*, *in* ISLAMIC ETHICS OF LIFE: ABORTION, WAR, AND EUTHANASIA, *supra*, at 81.

evangelical Protestants and (Eastern) Orthodox Christians, for example, do as well.[7]

First, *the status of fetuses and embryos*. Doerflinger considers the moral status of the human embryo in light of the historic conviction that each human individual has basic and equal human worth. No differences in talents or other conditions, including the stage of embryonic development, should overturn this evaluation. If we take the evaluation to heart, we infer that no one should be treated, exhaustively and without remainder, as a means or instrument. "The human individual, called into existence by God and made in the divine image and likeness . . . must always be treated as an end in himself or herself, not merely as a means to other ends . . . ."[8] It is cogent to infer inviolability too. To kill the innocent deliberately and directly is *the* prime instance of attacking such inviolability. Fetuses and embryos are assuredly innocent. Doerflinger sees both abortion and the destruction of embryos as treating fetuses and embryos merely as means to other ends, and as going against inviolability.

Second, *complicity*. Doerflinger assesses various arguments about complicity. Here, certain differences between abortion and the destruction of embryos *do* appear, but they give no comfort to the advocates of research on embryos.

> 1) Doerflinger grants that a researcher who uses fetal tissue is not necessarily a supporter of the decision to request or perform an abortion.
>
> 2) He refuses to say the same, however, about those who derive and use stem cells from embryos. "Here those who harvest and use the cells are necessarily complicit in the destruction of the embryo."[9]
>
> 3) He rejects as incoherent any claim that governmental funding of research on embryonic stem cells does not involve complicity in the destruction of embryos as long as researchers did not participate directly in such destruction.

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7. *See* Demetrios Demopulos, *Testimony of Father Demetrios Demopulos, Ph.D.*, *in* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 6, at B-1; Gilbert C. Meilaender, Jr., *Testimony of Gilbert C. Meilaender, Jr., Ph.D.*, *in* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 6, at E-1.

8. Richard M. Doerflinger, *The Ethics of Funding Embryonic Stem Cell Research: A Catholic Viewpoint*, 9 KENNEDY INST. ETHICS J. 137, 138 (1999); *see also* Gene Outka, *Respect for Persons*, *in* THE WESTMINSTER DICTIONARY OF CHRISTIAN ETHICS 541 (James F. Childress & John Macquarrie eds., 1986); Gene Outka, *Universal Love and Impartiality*, *in* THE LOVE COMMANDMENTS: ESSAYS IN CHRISTIAN ETHICS AND MORAL PHILOSOPHY 1 (Edmund N. Santurri & William Werpehowski eds., 1992).

9. Doerflinger, *supra* note 8, at 141.

> 4) He also criticizes the argument that derivation of stem cells from "spare" embryos donated by fertility clinics differs morally from using embryos created *solely* for research purposes, and that only the latter uses embryos as a mere *means* to other peoples' ends.

Third, *the alternative of adult stem cells.* Doerflinger, like many who endorse respect for human life from the earliest stages,[10] accents the advances that researchers have made in their work on adult stem cells. He also stresses a major advantage on which most agree: using adult cells avoids possible tissue rejection by treating a patient with his or her own cells. In the years since his article was published, however, claims have waxed and waned about the benefits of adult stem cell research.

B. Views in the Middle

First, *the status of fetuses and embryos.* We find a more liberal argument within the Catholic tradition and elsewhere that favors embryonic stem cell research. It requires us to distinguish between conception and individuation. Margaret Farley accepts this argument. For her and a number of other Catholic moral theologians, the human embryo is not considered

> in its earliest stages (prior to the development of the primitive streak or to implantation) to constitute an individualized human entity with the settled inherent potential to become a human person. The moral status of the embryo is, therefore (in this view), not that of a person; and its use for certain kinds of research can be justified. (Since it is, however, a form of human life, some respect is due it—for example, it should not be bought and sold.)[11]

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10. *See, e.g.*, Demopulos, *supra* note 7, at B-4 (discussing beliefs of the Greek Orthodox Church).

11. Margaret A. Farley, *Roman Catholic Views on Research Involving Human Embryonic Stem Cells*, *in* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 6, at D-1, D-4. In addition to the testimony already cited by Farley, Meilaender, and Demopulos, other testimony given to the National Bioethics Advisory Commission and published in 2000 displays the diversity of views within religious traditions. *See* sources cited *supra* notes 6-7; *see also* Edmund D. Pellegrino, *in* NAT'L BIOETHICS ADVISORY COMM'N, *supra* note 6, at F-1. While certain Catholic moral theologians hold divergent views on the moral status of the human embryo, the official teaching of the Catholic Church is that it is morally illicit to produce or use living human embryos for the preparation of embryonic stem cells. *See* Pontifical Academy for Life, Declaration on the Production and Scientific and Therapeutic Use of Human Embryonic Stem Cells, Aug. 25, 2000, http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20000824_cellule-staminali_en.html; CONGREGATION FOR THE DOCTRINE OF THE FAITH, INSTRUCTION *DIGNITAS PERSONAE* ON CERTAIN BIOETHICAL QUESTIONS (2008), *available at* http://www.usccb.org/comm/Dignitaspersonae/Dignitas_Personae.pdf.

Farley commends certain safeguards: for instance, donors may not specify who is to receive stem cells for therapeutic treatment, and an "absolute barrier" should be maintained between research and reproductive cloning. In this more permissive view, not everything is thereby permitted.

Second, *complicity*. Those who occupy positions in the middle may disagree about the moral standing of fetuses. Many, however, refuse to equate the destruction of embryos who already exist (but who will either be frozen in perpetuity or discarded) with the intentional creation and destruction of embryos solely to benefit third parties. Complicity in the former instance appears to be morally less grave. The decisive role here is played by those responsible for the existence of embryos in the first place and for electing subsequently to freeze them or discard them. Rather than initiating the creation or destruction of embryos, researchers react only after the responsible parties have reached their fateful determinations. The numbers of such embryos, effectively bereft of prospects, are vast. Some estimate that approximately 400,000 frozen spare embryos now languish in *in vitro* fertilization clinics.[12] The majority are no longer wanted or claimed by those who once needed them in order to have a child. Yet they retain final authority. Unless excess embryos are expressly donated, they will never be implanted. They will be *discarded*. Judging complicity should reckon with this datum accordingly.

Third, *the alternative of adult stem cells*. Those who occupy middle places across the spectrum generally accept (though sometimes reluctantly) a verdict that many scientists have reached. Stem cell therapies deriving from adults are necessary, but not yet sufficient, if we want to obtain the various cell types that clinically important areas of research require.

C. Views on the Left

First, *the status of fetuses and embryos*. Those who stand on the left side of the spectrum characteristically deny that the value accorded to pre-viable fetuses should ever override pregnant women's choices (for whatever reason) to terminate their pregnancies. Here I refer mostly to the works of John C. Robertson.[13] Robertson judges that to attribute basic and equal human worth to each human individual requires more than the presence of cells that have the potential to develop into the person. He refuses to say, however, that because embryos lack moral status in their own right we may do anything at all with them; they are not "means" to this extent. For example, we may not use them

12. Anne Drapkin Lyerly & Ruth R. Faden, *Willingness To Donate Frozen Embryos for Stem Cell Research*, 317 SCIENCE 46 (2007).

13. *See, e.g.*, John A. Robertson, *Ethics and Policy in Embryonic Stem Cell Research*, 9 KENNEDY INST. ETHICS J. 109 (1999). For a similar view on the left, see BONNIE STEINBOCK, LIFE BEFORE BIRTH: THE MORAL AND LEGAL STATUS OF EMBRYOS AND FETUSES (1992).

"for toxicology testing of cosmetics or buying and selling them."[14] One should deny intrinsic value to embryos and still accord them "symbolic" value and "'special respect' because of their potential, when placed in a uterus, to become fetuses and eventually to be born."[15] This symbolic value should nevertheless be trumped when we pursue a good scientific or medical end that we cannot pursue by other means. The value is thus extremely thin; it does not come to much.

Second, *complicity.* Robertson thinks that any distinction between the derivation and the use of embryonic stem cells does not survive critical scrutiny.[16] Researchers who use stem cells derived from embryos are complicit in their destruction, regardless of whether they participate directly in the destructive act. Moreover, those who support the use of cells from spare embryos from *in vitro* fertilization clinics should also support the creation of embryos for the purpose of research. In both cases, embryos do become a means to address the needs of others, once one decides to use them in research. Robertson displays an ironic affinity with Doerflinger on this matter. Both insist on an either/or choice, but draw the opposite normative conclusions. Either one should stop opposing the creation and destruction of embryos for research purposes only (in Robertson's view), or one should oppose not only the creation and destruction of embryos for research purposes, but also the research on spare embryos from in vitro fertilization clinics (in Doerflinger's view). On this point, both the left and right perspectives exert pressure on the middle point of view.

Third, *the alternative of adult stem cells.* Those who take Robertson's position can only prefer limiting research to adult stem cells if such a limit will in fact yield superior therapeutic benefits for members of society generally. They deny that the benefit of such a limit has been demonstrated.[17]

II. MORAL ASSESSMENTS

I commend as a normative point of departure the conviction that Doerflinger cites: "the human individual, called into existence by God and made in the divine image and likeness, . . . must always be treated as an end in himself or herself, not merely as a means to other ends . . . ."[18] Many hold this conviction, not only those on the right. To regard each person for his or her own sake, as one who is irreducibly valuable, authorizes a sphere of inviolability and heightens sensitivity

14. Robertson, *supra* note 13, at 117

15. *Id.* at 118.

16. *Id.* at 113.

17. A fourth point where controversies recur has two levels. The first concerns controversies about federal funding of stem cell research. The second level concerns controversies about the absence of coordination between research permitted in the public and private sectors. I find it disquieting that research possibilities lack any sort of society-wide oversight.

18. Doerflinger, *supra* note 8, at 138.

to the multiple ways we may go wrong. An approach that affirms inviolability and abjures domination captures deeply important commitments, which direct moral attention along lines I take to be permanently valid.

Many likewise draw on the language of ends and means to evaluate cases of "killing and saving."[19] Murder is arguably the quintessential instance of going wrong. Those who murder arrogate to themselves a position of false superiority. They usurp or perversely imitate God, who alone is the "Author of life and death." Murderers do their victims *incommensurable* harm; in depriving victims of life, they reduce their victims to "mere means" to their own aims and projects. Is it coherent to claim that actions that destroy embryos, such as abortion and embryonic stem cell research, are morally indistinguishable from murder?

Posing so blunt a question concentrates our thoughts. Yet it also encourages an unfortunate tendency to restrict evaluative possibilities to a single either/or. Either we judge abortion and the destruction of embryos to be *transparent* instances of treating fetuses and embryos as mere means to other ends. Or we judge abortion and embryonic stem cell research as morally *indifferent* actions *in themselves*, to be evaluated *solely* in terms of the benefits they bring to others. I reject what I take to be this simplifying restriction.

My own view is that the most fitting place to inhabit is a *particular* region in the middle. Unlike that of conservatives, my view does not extend the prohibition of murder to the prohibition of abortion and embryonic stem cell research.[20] And unlike that of liberals, my view ascribes an importance to fetuses and embryos that cannot be reduced to mere symbolism or the benefits that research on them may bring to third parties. This view can be illustrated on its own terms and in connection with formidable arguments on the right and left. The most distinctive example of the view I advocate is a simultaneous allowance of research on "excess" *in vitro* embryos and a rejection of the creation—for example, through research cloning—of embryos for research.

A. From the Right: Specificity and Stringency

The tradition of moral reflection that shapes conclusions on the right elevates two considerations that those in the middle should heed as well. One consideration is moral *specificity*. Murder is prohibited, but not all killing is murder. How shall we discriminate? We should not do so by writing morally evaluative references into the characterization of what murder is. The prohibition of killing in the Decalogue is construed more precisely to mean that we should

19. *See, e.g.*, JOHN P. REEDER, JR., KILLING AND SAVING: ABORTION, HUNGER, AND WAR 58-66, 164-68 (1996).

20. Though in the latter case I distinguish between engaging in research on cryopreserved embryos and intentionally creating and destroying embryos for research, it is the former whose meaning differs from murder. *See infra* note 30.

not intentionally kill innocent human life. This construal specifies what "murder" is. It is a delimited action-kind. The judgment that murder in *this* sense is wrong purports to be true yet is not a tautology. It is the judgment under scrutiny, and it remains possible to dispute it. To construe more precisely the prohibition of killing introduces on the one hand a certain flexibility. It helps to make sense of society's organized efforts to provide security for its citizens against arbitrary, unprovoked, or otherwise unjust assaults on life and limb, and to accommodate policing, courts of law, and soldiering. Yet on the other hand, this construal limits flexibility. When we meet cases that fall within its range of applicability, as we surely do, we may not then redescribe them at will. Instead, we acknowledge the moral features of the case we confront and either condemn or seek special justification or mitigation.

A second consideration is moral *stringency.* To reiterate an ancient question: may we (ever) do evil to achieve good?[21] When we meet cases that fall within the prohibition's range of applicability, we face two choices: the prohibition against killing as precisely construed possesses either *absolute* or *prima facie* authority in any circumstance to which it applies. Unless we understand how the prohibition against killing is construed, and that it may be accorded absolute authority, we fail to grasp where and why many on the right judge abortion and embryonic stem cell research as they do, and where and why many on the left demur.

Those on the right judge that the prohibition of murder extends to fetuses and embryos. Both are *innocent*, and aborting a fetus and disaggregating an embryo are *direct* actions that kill. Whether death is strictly *intended* is a more complicated question I think in the case of abortion. As for "human life," the last part of the specified prohibition, those on the right maintain that each human entity, from the time of conception, is irreducibly valuable. Indeed, each is judged to have an equally protectable status. If embryos are currently genderless and removed from the naked eye, they differ from the rest of us in that they await implantation, growth, and subsequent entry into the world of social interaction. But they contain the requisite genetic information that renders each unique.[22] And *all* of us began at this stage. Why then discriminate? Does our self-absorption blind us to injustices we may commit because at present we enjoy superior power? Assuredly, fetuses and embryos cannot now fight back on their own behalf. Yet *none* of us could at the point of our origins. To intervene and destroy fetuses and embryos palpably instrumentalizes them for the sake of those who are presently stronger. We do well to remember what our parents did, and that we are grateful for what they did, when we evaluate abortion and embryonic stem cell research.

Those on the right go next from specificity to stringency. We should make

21. *See* DOING EVIL TO ACHIEVE GOOD (Richard A. McCormick & Paul Ramsey eds., 1978).

22. Andrew Sullivan, *Only Human*, NEW REPUBLIC, July 30, 2001, at 8.

others' ends our own, *provided that these ends are morally permissible.* Violating the prohibition against killing as precisely construed *is* an impermissible end. We may not do or approve *this* evil, even when it achieves good. For we should always relate any benefits we aim to secure to what we are prepared to do to obtain them. We do best to consider *first* what *we* do and forbear, and not simply what will *happen*, and to live within the absolute limits that the prohibition against murder sets for us.

B. In the Middle: When "Nothing is Lost"

I have identified arguments from the right that I find formidable. Indeed, I think that what constitutes a human individual, and where his or her innocence still incontestably obtains, starts at conception. That embryos possess the requisite genetic information rendering each unique suffices to regard each as irreducibly valuable. To withhold such regard until the possibility of twinning is past, and to disqualify all embryos from this regard rather than include any resultant twins within its reach as well, seems to me to fall victim to greater arbitrariness. And I worry that when we possess superior power, we are tempted toward injustices that we decry when we lack power and commit when we enjoy it. Why, then, do I not simply accept these arguments without further ado?

Two lines of further argument move me from the right to the "right of middle." They prevent my saying that abortion and embryonic stem cell research are morally indistinguishable from murder. The first is an argument from "potentiality" that I discuss in detail elsewhere.[23] I now propose to invoke and

23. GENE OUTKA, THE ETHICS OF LOVE AND THE PROBLEM OF ABORTION, SECOND ANNUAL JAMES C. SPALDING MEMORIAL LECTURE 8-10 (1999) (printed in booklet form by the School of Religion, University of Iowa). In brief, I identify respects in which debates about abortion and debates about stem cell research converge and diverge. I also indicate how such debates pressure those in the middle in contrary directions. For example, some are disposed to be more permissive about embryonic stem cell research than about abortion for these reasons: a) Prior to implantation, we may distinguish conception from individuation, b) after implantation, the fetus is indeed a "power underway," who left to self-elaborating processes is likely to become "one of us." Abortion actively intervenes to terminate "a force that is there," and has the burden of proof, whereas an embryo must still be implanted, and until it is, we cannot describe it as now a self-elaborating power underway. Others are disposed to be less permissive about embryonic stem cell research than about abortion, reasoning that abortion may involve bona fide conflicts between two entities who are both ends in themselves, whereas embryonic stem cell research is morally simpler. It concerns only one such entity about whom we can say with certainty, here and now, that the action we take, disaggregation, causes incommensurable harm. That third parties may benefit from the research subsequently done, is an outcome for which we fervently hope. But such benefit lies in the future. It does not lend itself to similarly determinate judgment. And we cannot gainsay the possibility that it may be attained without taking any lethal step, e.g., through research on other, morally unambiguous sources of stem cells (from adults, umbilical cord blood, amniotic fluid, and

extend a second argument: the *nothing is lost* principle. I first learned of this principle from Paul Ramsey. While he was committed to an absolute prohibition against murder as the intentional killing of innocent life, he was prepared to attach two *exempting conditions* to it. One *may* directly kill when two conditions obtain: 1) the innocent will die in any case, and 2) other innocent life will be saved.[24] These two conditions stipulate what *nothing is lost* means. They originally extend to parity-conflicts, where one physical life collides directly and immediately with another physical life, and we cannot save both. I will argue that it is correct to view embryos in reproductive clinics who are bound either to be discarded or frozen in perpetuity as innocent lives who will die in any case, and those third parties with Alzheimer's, Parkinson's, and other diseases as other innocent lives who may be saved, or at least helped, by virtue of research on such embryos. I grant that this extension stretches the *nothing is lost* principle toward the outer limits of its application. For I defend the extension as a move to the effect that 1) nothing *more* is lost, and 2) *less* is lost, or at least, *someone* may be saved, or immensely helped (when clinical applications are attained). One reason it is worth considering is that we face a particular instance of a general phenomenon, namely, that novel developments arise, for which no clear precedents suffice to guide us in a wholly straightforward way. We should seek both to extend traditional moral commitments and to incorporate new developments as cogently as we can. To labor the obvious, some of the controversies we are examining only made sense *after* the age of *in vitro* fertilization dawned. *It* stands behind us, amplifying questions about "end" and "means" that our forebears could not foresee. Unless we are prepared to repudiate *in vitro* fertilization as such, so that we sympathize with infertile couples but refuse them a *right* to overcome their condition by any means that science and their financial resources make available, we must take the moral measure of these new possibilities.

In the instance before us, I sympathize with the plight of infertility but am disquieted by the way *in vitro* fertilization is practiced in our culture.[25] But rightly or wrongly, "excess" embryos are a tenacious datum, for they are a result of the practice as it currently exists. I welcome the day when such necessity vanishes, and welcome in the meantime "adopting" mothers willing to implant

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other possibilities discussed in PRESIDENT'S COUNCIL ON BIOETHICS, ALTERNATIVE SOURCES OF HUMAN PLURIPOTENT STEM CELLS 8 (2005), *available at* http://www.bioethics.gov/reports/white_paper/alternative_sources_white_paper.pdf).

24. PAUL RAMSEY, WAR AND THE CHRISTIAN CONSCIENCE: HOW SHALL MODERN WAR BE CONDUCTED JUSTLY? 171-91 (1961).

25. Sondra Wheeler led me to see that the normative position I defend requires a critical assessment of *in vitro* fertilization as currently practiced in the United States, and I thank her for perceptive counsel.

embryos when the genetic couple consents.[26] Not to welcome these things belies the claim that embryos as well as fetuses are irreducibly valuable. Nevertheless, embryos in appreciable numbers have now been discarded or frozen in perpetuity. *They will die, unimplanted, in any case. Nothing more will be lost by their becoming subjects of research.* Again, it is the absence of prospects of *these* innocents that partly extends the first exempting condition. It is the enhancement of prospects to *other* innocent life that partly extends the second exempting condition. *Less will be lost, or at least, someone may benefit.* These judgments taken together summarize the case I wish to make.

I say "partly." I do not say "wholly" and certainly not "transparently." The case for extension I put forward shows both continuities and discontinuities with prior judgments on the ethics of direct killing. I take the prior judgments seriously and extend them to novel possibilities as far as I can. But I acknowledge that the present debates attest to a moral space embryonic stem cell research occupies that is to a degree unprecedented. Let me give two examples of continuities and discontinuities.

First, consider this point of continuity. My extension goes so far, and no further. It includes embryos conceived to enhance fertility, but who will never be implanted. It excludes embryos created exclusively for research—as in research cloning—where we intentionally create them, and embrace their disaggregation as part of what *we do*. This limited extension accords with the timbre of *nothing is lost* in that we encounter circumstances we did not initiate and that we wish were otherwise. That we contemplate doing repellent things that we would not do for their own sake indicates that intentional killing was not "part of our plan" from the start. This timbre matters, yet a difference presents itself even here. The parity-conflict cases assume a contingent disaster that no one intends or foresees,

26. It is important to qualify any generalization that the creation of spare embryos is endemic to *in vitro* fertilization procedures as such. Consider the case of Germany since the passage of the 1990 Embryo Protection Act. *See* Gesetz zum Shutz von Embryonen [Act for Protection of Embryos], Dec. 19, 1990, BGBl. I, 69 at 2746 (F.R.G); Henning M. Beier & Jacques O. Beckman, *German Embryo Protection Act (October 24, 1990)*, 6 HUM. REPROD. 605 (1991). Germany allows during an *in vitro* fertilization procedure only the number of embryos to be developed beyond the pronucleus stage that will later be transferred. And three is the maximum number of transfers permitted. The striking result is that Germany faces no "plight" of excess embryos. To be sure, there is a drawback. Success rates are lower than they are in the United States. Nevertheless, I conclude two things. First, the normative position I espouse here effectively pushes closer toward the policies that Germany follows. These would require, however, a degree of regulation that is needed but missing in the United States. Second, this same normative position requires that I attend to the large number of excess embryos that exist already in the United States and in certain other countries. Their "plight" is a *fait accompli*. The "nothing is lost" appeal that I invoke pertains chiefly to their plight. To ignore the existence of these excess embryos, to fail to reflect on their significance, would subtly belittle the moral quandaries they pose. I am indebted to Sabine Hermission for information about policies in Germany.

nor is it made part of any established procedure. "Excess" embryos are foreseeable and endemic to the *in vitro* fertilization procedure to date. At a minimum, we foresee this. Still, we intend *in performing* the procedure to alleviate infertility, not to create embryos for research. Thus a significant continuity holds, despite this difference.

Second, consider this point of discontinuity. The *nothing is lost* principle, as originally formulated, is narrower and more exact than an extension to the novel case of unimplanted embryos can be. In parity-conflict cases that goad us to articulate the *nothing is lost* principle in the first place, unless we directly kill one, we cannot save the other, and this allows us to claim that we *would* save both if we *could*. In cases of unimplanted embryos, we face no similar temporal and causal limits. No other party will directly and immediately die if we elect to save embryos by freezing them. Any "conflict" is much further removed and comparatively indeterminate, plainly from parity-conflict cases, and arguably from abortion decisions more generally.

C. From the Left: Derivation and Use, and Ends and Means

As argued above, Doerflinger on the right and Robertson on the left defend an either/or dichotomy that I in the middle reject. They hold respectively that *either* we should oppose both the creation and destruction of embryos for research purposes and the research on spare embryos from *in vitro* fertilization clinics, *or* we should stop opposing the creation and destruction of embryos for research purposes only. I develop my view further in relation to two considerations that Robertson and those on the left raise.

Derivation and use: As noted previously in the discussion of "complicity," Robertson makes two claims that we should not conflate. He contends first that the distinction between derivation and use is chimerical. Researchers are complicit in destroying embryos when they use stem cells derived from them, whether or not they engage in the actual destroying themselves. So far, I agree. The earlier NIH Guidelines promulgated during the Clinton Administration[27] split the difference, perhaps for political reasons, to promote civil peace by not ignoring conservatives' concerns altogether, but funding research all the same. Second, Robertson contends that if one supports research on embryos obtained as "spares" from *in vitro* fertilization clinics, one should also support creating and destroying embryos for the purpose of research. For embryos *do* become a "mere means," once we decide to use them in research. I think we may compatibly accept his first contention and reject his second. And if I am right to extend in a qualified way the *nothing is lost* principle, we have important reasons to reject the second.

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27. *See* National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells, 65 Fed. Reg. 51,976 (Aug. 25, 2000).

Ends and means: Reasons based on ends and means focus on the status we ascribe to embryos, and on how we interpret the injunction to treat persons as ends in themselves. Robertson holds, along with many others, that embryos are too rudimentary to have moral status in their own right. He ascribes "symbolic" value to them (for example, they may not be bought and sold), but states that they lack "intrinsic" value. The account of potentiality I offer elsewhere[28] and of irreducible value offered above *does* ascribe status to them in their own right. Potentiality is more than mere possibility. It is a power underway, and more so with fetuses than with embryos. Yet in both cases potentiality includes *existent* capacities to *acquire* in the future various characteristics typically attributed to those who "bear the human countenance"—e.g., self-awareness, personal accountability, and conscious relations with other human beings. I intend potentiality to be robust enough, in the case of both fetuses and embryos, to resist the view that fetal life and embryonic life lack any weight *as soon as* they conflict with other interests. Without such resistance, we reduce concern for such life to a platitude, a mere expression of good will that never has efficacy and can always be trumped.

Again, Robertson insists that once we decide to use embryos in research, they do become a "mere means." This announces moral equivalence between two circumstances that I have argued differ relevantly. It is one thing to say that innocent life "will die" in any case, when one refers to a condition that one did not, by one's own hands, bring about, and that in most instances one cannot alter. It is another to say that innocent life will die at one's own hands, a condition that one plans and brings about from the beginning, and where one could have done otherwise. This latter procedure does reduce embryos to a menial status. We would distort the *nothing is lost* principle beyond recognition if we extended it to say that nothing is lost when we create an entity whose prospects are nil because of what we intend from the start.

Robertson's position leads me to ask how much remains of the injunction to treat persons as ends in themselves when we allow research on frozen and eventually-to-be-discarded embryos. Some seek to bear witness to the dignity of embryos by refusing to do anything to them other than freeze them. They adhere to the norm that one does best to consider *first* what one does and forebears, and not simply what will *happen*. Although I find this norm persuasive across a range of other circumstances, I find here that such a witness threatens to idle. It is difficult to specify what interests one *protects and promotes*, for example, when freezing and discarding are all that one can seriously envisage. To honor potentiality where there is no hope of implantation is to honor perpetual potentiality.[29] What one can and cannot do in treating persons as ends will be

28. *See* OUTKA, *supra* note 23.

29. Brian Sorrells suggested this phrase while reading an earlier draft and I gratefully appropriate it. That honoring in this case threatens to idle distinguishes it from another sort of case

affected by *their* prospects. Love for an embryo who will live at most in a perpetually frozen state without self-awareness, has less prospective room than love for a fetus who is a power underway and who *will* acquire self-awareness by virtue of his or her self-development. What we can envisage and do, now and later, has greater scope in the latter instance, which is why termination obliterates a future that the fetus now *has* in prospect, a future that an embryo frozen in perpetuity itself still *lacks*.

The injunction retains some force, however, as we disallow the intentional creation and destruction of embryos as in the case of research cloning. In so doing, we draw more closely together the moral considerations we weigh in judging the permissibility of research on fetal cadavers and certain-to-be-discarded embryos. In both cases, the genetic parents decide whether to donate them for research. Researchers play a lesser role (they lack a voice in the decision to abort or to attempt *in vitro* fertilization) than when they guide the intentional creation and destruction of embryos.

To extend the *nothing is lost* principle in the way I do sets a deontological constraint on "sources" that applies in principle to stem cell research in the public and private sectors. It draws a line between research on embryos created solely for this purpose in research cloning, and research on embryos from *in vitro* fertilization clinics slated to be discarded or frozen in perpetuity. It disallows the first sort of research and allows the second. This constraint makes concern about

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to which I think the "nothing is lost" appeal does not apply. The latter sort of case assumes a difference between destruction of an entity for body parts because that entity will die in any event and using cells from an entity already dead. Some may worry that "nothing is lost" may allow the general "harvesting" of organs or tissues from the living who are, for example, terminally ill, permanently comatose, or condemned to die by authorities of the state as criminals. The specter of Nazi doctors may well appear: if certain people are slated for death anyway, why not experiment on them to the point of ending their lives to acquire knowledge? (Gilbert Meilaender helpfully posed this question to me in correspondence.) "Nothing is lost" does not apply to this sort of case. It is *impermissible* to destroy any entity for body parts who has an agential history even if he or she does not now have any considerable future, e.g., entities whose maturity deprives their genetic parents of authority to end their existence or to elect to donate them for research. Moreover, the Nazi-doctor analogy fails because even research on camp inmates allows for significant alternatives. Not only is it less than absolutely certain that the victims will die, but victims condemned may still be shown kindness and consideration. These alternatives need not and should not be lost. But we lack any way of showing human kindness to cryopreserved embryos. John Reeder observes in quoting Baruch Brody that "[t]he basic point of nothing is lost is that, as Brody puts it, the one to be killed does not 'suffer any significant losses . . . in unrealized potential.'" REEDER, *supra* note 19, at 62-63 (quoting BARUCH A. BRODY, ABORTION AND THE SANCTITY OF LIFE: A PHILOSOPHICAL VIEW 151 (1975)). I claim that "unrealized potential" carries for the embryos in question *distinctive* finality that resists generalization. (I am indebted to John Reeder, Richard Fern, and Oliver O'Donovan for discussion of when "nothing is lost" applies and does not apply.)

embryos more than an ineffectual afterthought. We should leave the line intact and be content to derive as many scientific and medical benefits from research on "excess" embryos as we can.[30]

The constraint matters then as it marks the drawing of a line. It matters in a further way. It registers an attitude of ongoing mourning for a plight. We regard research even on excess embryos as something to which we only reluctantly acquiesce. This attitude begins in sympathy for those who view their own infertility as an affliction they seek to overcome. It continues in allowing unprecedented *in vitro* technology that sometimes triumphs over this affliction. But such technology brings one outcome we foresee and lament: namely, the presence of excess embryos to be discarded or frozen in perpetuity. The case for extension occurs, once more, in circumstances I take as lamentable. We welcome neither infertility nor excess embryos. The attitude concludes in a desire that one day we may get out and get out for good. That is, we look forward to a time when we may reprogram adult stem cells or otherwise obtain alternative sources of human pluripotent stem cells so that we no longer require embryos as a source.

Such looking forward disposes me to welcome efforts to obtain pluripotent, genetically stable, and long-lived human stem cells that do not require creating,

30. Unless we attempt *in practice* to honor this line, we jeopardize the importance of a moral distinction that shows how research cloning *does* instrumentalize in a thoroughgoing way. William FitzPatrick astutely draws on the intend/foresee distinction to demonstrate this. "In the case of research cloning, the relation between what is clearly aimed at—the embryo's being disaggregated to get stem cells—and the purported side effect—the embryo's being destroyed or killed—is 'too close' to allow for an intelligible application of the intend/foresee distinction." William FitzPatrick, *Surplus Embryos, Nonreproductive Cloning, and the Intend/Foresee Distinction*, HASTINGS CENTER REP., May-June 2003, at 29, 32. Yet I want to accord greater practical stringency than he does to his assessment that research cloning assumes "an *intrinsically inappropriate* attitude toward the beginning stages of human life" that the intend/foresee distinction brings out. *Id.* at 36. He judges instead that his assessment "lacks sufficient moral weight to warrant opposing cloning in the end." *Id.* at 34. Although he subsequently rebuts several "slippery slope" arguments to which his allowing cloning are alleged to lead, these consequentialist considerations lack the power of his earlier deontological assessment. *Id.* at 35. The point at which I think we may allow room for maneuver concerns the *distinct* practice of *in vitro* fertilization and cryopreservation of embryos. To invoke the "nothing is lost" principle *here* means roughly this: we are *given* a situation (many embryos are *currently* frozen in perpetuity). We cannot argue about it, whether or not we lament it. We must decide in the constrained field that has resulted. "To abstain from research on cryopreserved embryos" hardly has the same meaning as "to abstain from murder." But "intentionally to create and destroy embryos for research" has a meaning too similar to murder: something is lost, deliberately by our own hands, and we treat what is lost entirely as a means. And so I oppose two discrete kinds of idling. It is idling to refrain from attempting to honor in practice how the intend/foresee distinction applies to research cloning. It is idling to do nothing but allow cryopreserved embryos to languish unregarded and doomed, where we cannot show them positive kindness or otherwise affect their certain prospects.

destroying, or harming human embryos. The President's Council on Bioethics, in a recent white paper,[31] has canvassed most usefully four possible approaches, and Rajesh Rao's Article in this issue describes these and other alternatives to embryos.[32] I cannot viably consider the ethical debates surrounding these alternative sources in this Article. But I judge that an appeal to "nothing is lost" can accommodate three of the sources. These are the following: deriving cells from organismically dead embryos; deriving cells from specially engineered biological artifacts (though confining experimentation at present to animal models); and obtaining cells by somatic cell dedifferentiation (also known as "reprogramming" or inducing pluripotency). The fourth approach, extracting blastomeres from living embryos, imposes too many risks on living embryos to satisfy the "nothing is lost" principle.[33]

CONCLUSION

The subject of stem cell research remains volatile. We should beware of assuming here that once we turn to institutional policies, we no longer need to engage in "theoretical" debates. On this subject, we are never done with moral points of departure. These determine, in key part, what we take desirable and undesirable institutional policies to be. We make claims as I have done here, weighing arguments about where to place ourselves along a spectrum, how far judgments about abortion and stem cell research diverge, and so on. If we give these enduring moral concerns short shrift, we enter the political fray with undefended assumptions that we merely announce.

To avoid such an outcome, we must not grow weary of moral debates. They matter, and moral views exert vast influence. Between those who evaluate embryos as equally protectable human life and those who evaluate embryos as only "clumps of cells in Petri dishes," there is no peace. I have tried to suggest why neither of these evaluations is adequate. And I for my part then must continue to attempt to address conservative and liberal objections.

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31. PRESIDENT'S COUNCIL ON BIOETHICS, *supra* note 23.

32. *See* Rajesh C. Rao, *Alternatives to Embryonic Stem Cells and Cloning: A Brief Scientific Overview*, 9 YALE J. HEALTH POL'Y L. & ETHICS 603 (2009).

33. For a detailed review of these conclusions, I am indebted to a paper that Carolyn Brokowski kindly sent me in response to my attempt to apply the "nothing is lost" principle. For further detailed scrutiny, see DOMESTIC POLICY COUNCIL, ADVANCING STEM CELL SCIENCE WITHOUT DESTROYING HUMAN LIFE (2007), *available at* http://www.montegen.com/Montegen/Nature_of_Business/The_Library/Genomics/Stem_cells/stemcell_010907.pdf. Special note should be taken of "induced pluripotent stem cells," or "iPS cells." "These techniques not only avoid any ethical concerns . . . but they offer a far cheaper and easier method of producing genetically matched or selected pluripotent stem cells, which makes them appealing to researchers. As a result, this technique has begun to overtake the use of embryos in many stem-cell labs." Levin, *supra* note 3, at 17.

I object to the sort of embryonic stem cell research that creates embryos for the sake of benefits to third parties, where one *embraces* the disaggregation of embryos as *necessarily* part of what one *does* from the beginning. To conduct this research clashes directly with the judgment that entities conceived have irreducible value. For it is one thing to allow that we need not yet ascribe full moral standing or equal protectability to embryos. It is another thing to "instrumentalize" them through and through when what we intend *in* the actions we perform *exhaustively* concerns benefits to *third* parties. But the claims also indicate why I object to an ironic alliance that those on the right and left sometimes form, to the effect that we should either forbid or permit all embryonic stem cell research. There is, I believe, a more nuanced possibility, where we may distinguish *creating* for research and only *employing* for research. The latter allows us to consider the tangled aftermath of *in vitro* fertilization as a practice in our culture. Employment for research connects with the datum of discarded embryos, where the original creation of embryos possesses a non-instrumentalist rationale (namely, the promotion of fertility), so that what we intend does not exhaustively concern benefit to third parties. The aftermath for discarded embryos allows us to pursue benefits to third parties when we may do so without, from the start, creating embryos and where we embrace their disaggregation as necessarily part of what we do. These differences lead me to argue that the *nothing is lost* principle illuminates a morally significant distinction between creation for research and employment for research. That both houses of Congress have twice passed bills along these very lines, which were vetoed by President Bush, indicates that many on the left and the right consider this a cogent moral position that should be given political and legal effect.[34] Whether or not the Congress under President Obama abandons this distinction *de facto*, it still retains moral force.

34. The first bill was the Stem Cell Research Enhancement Act of 2005, which the House passed in May of 2005. In July on 1996, the Senate also passed the act, but Bush vetoed it the same month. *See* Stem Cell Research Enhancement Act of 2005, H.R. 810, 109th Cong. (2005). The second bill was vetoed in June of 2007. *See* Stem Cell Research Enhancement Act of 2007, S. 5, 110th Cong. (2007). The grounds for President Bush's opposition to both bills flow from his August 9, 2001 speech on stem cell research. I note however that I developed my argument on the analytical and moral merits of the case well before these events, in an article whose substance I extend here. Gene Outka, *The Ethics of Human Stem Cell Research*, 12 KENNEDY INST. ETHICS J. 175-213 (2002). Christiana Peppard and Brian Sorrells have encouraged me to register these political developments, and for this and other suggestions I have incorporated, I thank them both.

Alternatives to Embryonic Stem Cells and Cloning: A Brief Scientific Overview

Rajesh C. Rao*

Advances in recent years have begun to elucidate the distinct mechanisms that maintain embryonic stem cells (ESCs) *undifferentiated, self-renewing,* and *pluripotent.* One of the "grails" of therapeutic stem cell biology is the ability to confer these special properties of the embryonic stem cell onto an easily accessible, differentiated cell from the adult (such as a skin or blood cell) without the creation of an embryo as a necessary intermediate step. Such a technology would not only provide an ethically acceptable alternative to research cloning, but it would also offer a method to interrogate the biological basis of "stemness," the constellation of gene expression and protein signaling that underlie self-renewal and pluripotency.

A landmark study published in 2006 and many subsequent reports demonstrate that the reactivation of a handful of particular genes can "reprogram" a differentiated cell from a variety of rodent and human tissues into a cell with several properties of embryonic stem cells, including self renewal and pluripotency.[1] These reports demonstrate that much of the "grail" has now been found, albeit with some important limitations. A number of studies have successfully demonstrated the viability of theoretical proposals previously offered by President Bush's Council on Bioethics to generate alternative sources of pluripotent cells, at least in the experimental setting.[2] These promising

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1. Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663 (2006); *see also* Takashi Aoi et al., *Generation of Pluripotent Stem Cells from Adult Mouse Liver and Stomach Cells*, 321 SCIENCE 699 (2008); Alexander Meissner, Marius Wernig & Rudolph Jaenisch, *Direct Reprogramming of Genetically Unmodified Fibroblasts into Pluripotent Stem Cells*, 25 NATURE BIOTECHNOLOGY 1177 (2007); Keisuke Okita et al., *Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vectors*, 322 SCIENCE 949 (2008); Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861 (2007); James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145 (1998); Marius Wernig et al., *A Drug-Inducible Transgenic System for Direct Reprogramming of Multiple Somatic Cell Types*, 26 NATURE BIOTECHNOLOGY 916 (2008).

2. *See, e.g.*, Davor Solter, *Politically Correct Human Embryonic Stem Cells?*, 353 NEW ENG. J. MED. 2321 (2005).

advances stand in stark contrast to the earlier revelation that reports of highly efficient derivation of several new human ESC lines through research cloning by South Korean researchers were false.[3] Nevertheless, it remains clear that clever and innovative efforts to generate pluripotent stem cells through research cloning as well as through alternative methods continue unabated.

In this Article, I discuss the recent development of "alternative" methods—that is, techniques that do not involve research cloning—to derive pluripotent stem cells, most prominently among them, induced pluripotent stem (iPS) cells. Here, easily obtainable differentiated cells may be genetically manipulated to revert the cell to a stem cell state, from which clinically desirable cell types can be derived.[4] Similarly, a "parthenote" (derived entirely from one parent) that does not have the potential to develop into a person might be a source of cell lines with potential comparable to that of embryonic stem cell lines. Ironically, this is what was proven to be the origin of the so-called "cloned" human embryonic stem (ES) cell lines claimed by South Korean researchers in 2005.[5]

This overview will focus primarily on the scientific developments and challenges of alternative sources of stem cells. In Part I, I will first review basic facts of cell differentiation, reprogramming, and the epigenetic state. In Part II, I will discuss recent work in adult stem cells (ASCs), including ASCs derived from reproductive tissues. Part III will discuss the more ethically complex procedures of extracting embryonic stem cells from "dead" embryos, "living" embryos, and biological artifacts. Part IV investigates the possibility of using existing stem cell lines for further research, but modulating host immune responses and rejection when tissues derived from those lines are introduced into potential patients. Finally, Part V will address the most cutting-edge and scientifically promising alternatives of dedifferentiation and transdifferentiation, both of which involve reprogramming specialized cells.

I. REPROGRAMMING AND THE EPIGENETIC STATE

Before outlining developments in "reprogramming," it is important to review the basic processes of cell differentiation and reprogramming. Every somatic cell in the body harbors identical genetic information: each cell contains the same DNA, which encodes the same genes. Although each cell contains the same genes, the unique pattern of gene *expression* specifies each cell's unique identity, and differential gene expression is responsible for the diverse array of specialized

3. Donald Kennedy, *Editorial Retraction*, 311 SCIENCE 335 (2006).

4. *See, e.g.*, Takahashi et al., *supra* note 1.

5. *See* Woo S. Hwang et al., *Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts*, 308 SCIENCE 1777 (2005); Kitai Kim et al., *Recombination Signatures Distinguish Embryonic Stem Cells Derived by Parthenogenesis and Somatic Cell Nuclear Transfer*, 1 CELL STEM CELL 346 (2007).

cell types that constitute the organism. Gene expression is regulated by chemical modifications to DNA and DNA-associated proteins called histones, which are proteins around which DNA is "wrapped." Methylation is a chemical modification to specific nucleic acids on DNA that "silences" certain genes by preventing proteins called transcription factors from accessing crucial activating sequences of a gene.[6] Transcription factors enable expression of a particular gene on the relaxed segment of DNA. Acetylation, phosphorylation, methylation, and other chemical modifications of histones play central roles in regulating gene expression. Importantly, these modifications of DNA and histones do *not* alter the sequence of DNA.

Specific patterns of these DNA and histone modifications define the *epigenetic state* of the cell, namely the cumulative chemical modifications that determine the unique constellation of gene expression, and consequently, cell type. Embryonic stem cells appear to have a distinctive epigenetic state, especially with regard to patterns of histone methylation.[7] Namely, large stretches of DNA are marked by a type of histone methylation associated with gene repression. Interestingly, within these regions are smaller domains in which genes harbor a type of histone methylation associated with gene expression. Many of the genes that encode developmentally regulated transcription factors display such "bivalent domains" and are expressed at low levels. One theory is that such domains allow silencing of tissue-specific transcription factor expression while simultaneously being "poised for activation" during subsequent differentiation.[8]

Reprogramming refers to the process by which a differentiated cell converts to another type of cell. The mechanisms underlying reprogramming thus involve dramatic changes in the epigenetic state of the cell, enabling a unique pattern of gene expression that defines the reprogrammed cell. Examples of reprogramming include conversion of a differentiated egg cell into all embryonic and extra-embryonic (e.g., placenta) cell types following fertilization by sperm. Other means of reprogramming include induced pluripotency, parthenogenesis, cell fusion, chemical inductions, and the addition of specific subcompartments of one cell to another cell (e.g., the transfer of nuclei by somatic cell nuclear transfer, or the transfer of cytoplasm by ooplasmic transfer). Not surprisingly, these processes alter the epigenetic state of the cell.

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6. Takumi Takizawa et al., *DNA Methylation Is a Critical Cell-Intrinsic Determinant of Astrocyte Differentiation in the Fetal Brain*, 1 DEVELOPMENTAL CELL 749 (2001).

7. Bradley E. Bernstein et al., *A Bivalent Chromatin Structure Marks Key Developmental Genes in Embryonic Stem Cells*, 125 CELL 315 (2006).

8. *See id.*

II. ADULT STEM CELLS

To date, human adult stem cells (hASCs) are the most thoroughly researched alternative to human embryonic stem cells. Tissues generated from autologous (genetically identical) and allogeneic human embryonic stem cells (hESCs) are obviously not the only sources of stem cell transplants. There has been an explosion of clinical and preclinical studies demonstrating the ability of both hESCs and adult stem cells to repair degenerating and neoplastic tissue, as in multiple sclerosis,[9] spinal cord injury,[10] diabetes,[11] heart disease,[12] and cancer.[13] Tandem scientific developments in the field of hASCs—the derivation of which do not require an embryo source—will likely affect the fate of research cloning. Many opponents of hESC research believe that hASCs demonstrate all the clinically useful properties of the former without the ethically contentious process of stem cell extraction from the embryo. Therefore, many believe that hESC research should be banned or supplanted by hASC studies. Accordingly, hESC opponents have hailed each animal and human adult stem cell study that demonstrates potential therapeutic applications as evidence for the utility of hASCs over hESCs. Such assertions are often made despite clear differences in the differentiation, engraftment, and growth factor requirements among stem cell lines of particular sources. These differences highlighted to date imply medically optimal and appropriate uses for *both* types of stem cells under various clinical circumstances.

The category of adult stem cells is really an umbrella designation that includes all stem cells isolated from non-embryo or non-fetal sources. Generally hASCs have a more limited differentiation potential than hESCs. For instance, neural stem cells can develop into cell types that comprise the brain and spinal

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9. *See, e.g.*, Stefano Pluchino et al., *Injection of Adult Neurospheres Induces Recovery in a Chronic Model of Multiple Sclerosis*, 422 NATURE 688 (2003).

10. *See, e.g.*, Qilin Cao et al., *Stem Cell Repair of Central Nervous System Injury*, 68 J. NEUROSCIENCE RES. 501 (2002).

11. *See, e.g.*, Julio C. Voltarelli et al., *Autologous Nonmyeloablative Hematopoieitic Stem Cell Transplantation in Newly Diagnosed Type I Diabetes Mellitus*, 297 JAMA 1568 (2007).

12. *See, e.g.*, Stefan Janssens et al., *Autologous Bone Marrow-Derived Stem-Cell Transfer in Patients with ST-Segment Elevation Myocardial Infarction: Double-Blind, Randomised Controlled Trial*, 367 LANCET 113 (2006); Amit N. Patel et al., *Surgical Treatment for Congestive Heart Failure with Autologous Adult Stem Cell Transplantation: A Prospective Randomized Study*, 130 J. THORACIC & CARDIOVASCULAR SURGERY 1631 (2005); Deepak Srivastava & Kathryn N. Ivey, *Potential of Stem-Cell-Based Therapies for Heart Disease*, 441 NATURE 1097, 1097-98 (2006).

13. *See, e.g.*, Murielle Mimeault, *Concise Review: Recent Advances on the Significance of Stem Cells in Tissue Regeneration and Cancer Therapies*, 24 STEM CELLS 2319 (2006); Masamitsu Yanada et al., *Allogeneic Hematopoietic Stem Cell Transplantation as Part of Postremission Therapy Improves Survival for Adult Patients with High-Risk Acute Lymphoblastic Leukemia: A Metaanalysis*, 106 CANCER 2657 (2006).

cord and rarely, if ever, non-neural tissues. Hematopoietic (blood-forming) stem cells differentiate into all blood tissues and cells of the immune system. This limited specialization capacity is termed multipotency. In contrast, hESCs are pluripotent—that is, they have the capacity to differentiate into all somatic tissues. The actual age of the donor does not matter: hASCs isolated from a newborn, a teenager, or a sixty-year-old adult are all considered to be adult stem cells. Each tissue-specific hASC is generally isolated from a specific region of that tissue. For example, neural stem cells from a variety of species can be extracted from a certain region of the adult brain, termed the subventricular zone.

Adult stem cells isolated from patients offer autologous tissues for transplantation; because they are from the patient, no immunosuppressive drugs are required. However, with the exception of autologous and allogeneic hematopoietic stem cells, few other adult stem cells have been characterized well enough to permit their routine transplantation. Human mesenchymal stem cells (hMSCs), a type of non-hematopoietic adult bone marrow stem cell, have been evaluated in clinical trials as support for hematopoietic stem cell transplants for blood cancers[14] as well as bone fractures.[15] Some populations of hMSCs have been shown to engraft allogeneically (when the donor cells are *not* genetically matched to the recipient); according to evidence obtained from a fetal lamb model, there is little immune rejection.[16] Research groups have reported a wide differentiation spectrum, including clinically relevant cell types such as cardiomyocytes (heart muscle cells) and chondrocytes (cartilage-forming cells).[17] Therefore, hMSCs may offer an alternative to some types of hESC transplantation, especially if generation of autologous tissues from hESCs via research cloning proves too expensive. Moreover, even if cardiomyocytes

14. O.N. Koç, *Clinical Trials of Human Mesenchymal Stem Cells To Support Hematopoietic Stem Cell Transplantation*, *in* GENETIC ENGINEERING OF MESENCHYMAL STEM CELLS 151 (Jan A. Nolta ed., 2006).

15. Shannon M. Rush, Graham A. Hamilton & Lynn M. Ackerson, *Mesenchymal Stem Cell Allograft in Revision Foot and Ankle Surgery: A Clinical and Radiographic Analysis*, 48 J. FOOT & ANKLE SURGERY 163 (2009).

16. *See, e.g.*, Kenneth W. Liechty et al., *Human Mesenchymal Stem Cells Engraft and Demonstrate Site-Specific Differentiation After* In Utero *Transplantation in Sheep*, 6 NATURE MED. 1282 (2000).

17. *See, e.g.*, Sudeepta Aggarwal & Mark F. Pittenger, *Human Mesenchymal Stem Cells Modulate Allogeneic Immune Cell Responses*, 105 BLOOD 1815, 1815 (2005) ("[I]n vitro experiments demonstrated that clonal human MSCs are able to differentiate into various lineages including osteoblasts, chondrocytes, and adipocytes. In vitro and in vivo studies have also indicated the capability of MSCs to differentiate into muscle, neural precursors, cardiomyocytes, and possibly other cell types."); Hiroshi Kawada et al., *Nonhematopoietic Mesenchymal Stem Cells Can Be Mobilized and Differentiate into Cardiomyocytes After Myocardial Infarction*, 104 BLOOD 3581 (2004); Mark F. Pittinger et al., *Multilineage Potential of Adult Human Mesenchymal Stem Cells*, 284 SCIENCE 143 (1999).

derived from allogeneic lines of hESCs can be transplanted, the risks of long-term immunosuppression may favor an hMSC-based approach.

Neural cells derived from fetal and adult neural stem cells or hESCs may also have medical application without immunosuppression because the brain is largely an "immune privileged" site. That is, the brain does not reject transplanted cells, unlike most of the body. This property has enabled cell transplantation in clinical trials for patients with stroke and Parkinson's disease, some of which have precluded the need for immunosuppressive drug regimens.[18] The direct reprogramming of adult stem or differentiated cells to an ES-like state without a totipotent embryo intermediate would be the least ethically contentious alternative to hESCs and a potential source of unlimited, genetically matched cells for therapeutic use. Fortunately, this has now become a reality.

A. Pluripotent Cells Derived from Reproductive Tissues

A recent report described the generation of pluripotent, ES-like cells from the neonatal mouse testis.[19] As noted above, the ASC designation refers to stem cells present any time after birth. In this case, neonatal mouse testes were cultured in ESC-promoting cell culture conditions, and both *in vitro* and *in vivo* assays demonstrated that the resulting stem cells could contribute to all somatic tissues and were therefore pluripotent. It is not surprising that these germ cells are pluripotent, as certain germ cell tumors can contain tissues from all germ layers (such as neurons, teeth, and hair!). While the derivation of pluripotent cells from germ cells of wild-type older mice was not successful, germ cells from transgenic mice lacking a certain cell cycle gene could generate pluripotent ES-like cells. The authors suggest that modification of culture conditions or *in vitro* genetic manipulation of cells from the mature adult may make this process more efficient.

If it is possible to generate similar pluripotent cells from human reproductive tissues, such cells may be an ethically acceptable alternative to research cloning because no embryo is created. For instance, a child may undergo a testicular biopsy, from which germ cell-derived ES-like cell lines could be generated. Should the child need the specific tissues for future therapy, appropriate cells may be differentiated from the pluripotent line and grafted into the patient. Such a strategy is not without caveats. For example, the biopsy of testicular or other reproductive tissues carries certain risks, and it is unknown at this time how much tissue would be required to generate a pluripotent cell line. Also, even if

18. Curt R. Freed et al., *Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease*, 344 NEW ENG. J. MED. 710 (2001); D. Kondziolka et al., *Transplantation of Cultured Human Neuronal Cells for Patients with Stroke*, 55 NEUROLOGY 565 (2000).

19. Mito Kanatsu-Shinohara et al., *Generation of Pluripotent Stem Cells from Neonatal Mouse Testis*, 119 CELL 1001 (2004).

such tissues were grafted autologously, some degree of immune incompatibility due to the unique methylation patterns of tissues from germ cell-derived pluripotent cells will remain. However, autologous transplantation assays in animals could quickly provide some answers.

III. EXTRACTION OF EMBRYONIC STEM CELLS FROM "DEAD" AND "LIVING" EMBRYOS AND FROM BIOLOGICAL ARTIFACTS

Given that objections to hESC research often turn on the death of the embryo, researchers have sought alternative sources of hESCs that are more ethically acceptable, such as "organismically dead" embryos, "living" embryos destined for implantation, and biological artifacts. However, these sources do not always avoid the ethical arguments about the destruction of embryos.

A. "Dead" Embryos

Tissue donation from human cadavers remains an important clinical strategy for patients with some types of severe organ dysfunction. Provided proper consent, the use of organs from those declared dead is considered ethically acceptable. The utility of such a donation relies on the fact that while a person can be declared dead, certain organs and tissues may still be functioning at a level sufficient for successful transplantation into a patient. Similarly, some consider that an embryo can be "organismically dead," but can still contain functioning, individual cells. One definition for an organismic death of an embryo is cessation of "continued and integrated cellular division, growth, and differentiation."[20] When this happens, as is the case for many embryos derived via *in vitro* fertilization (IVF), the embryo would not develop any further *in vitro* and would not be viable following uterine transfer. Most IVF embryos are cultured to the 2-10 cell stage (2-3 days old) or up to the blastocyst stage (5-6 days old), and then transferred into the uterus. At the 2-8 cell stage, each component cell, called a blastomere, is totipotent. However, by 5-6 days following blastocyst formation, the inner cell mass—composed of the cells that are usually extracted to derive hESC lines—has formed and no individual cell is capable of full embryonic development. In other words, there are no longer any totipotent cells present.[21]

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20. This theory is primarily attributed to Donald Landry and Howard Zucker. *See* Donald W. Landry & Howard A. Zucker, *Embryonic Death and the Creation of Human Embryonic Stem Cells*, 114 J. CLINICAL INVESTIGATION 1184, 1185 (2004).

21. See G. Cauffman et al., *Markers that Define Stemness in ESC are Unable To Identify the Totipotent Cells in Human Preimplantation Embryos*, 24 HUMAN REPROD. 63, 64 (2009) ("The initial loss of totipotency occurs during preimplantation development and becomes apparent for the first time when two distinct cell lineages in the blastocyst segregate forming the inner cell mass . . . .").

In the case of organismic death of the early embryo (2-8 cell stage), for example, one may consider a case in which six of eight cells appear to have irreversibly ceased division. As highlighted by some members of the President's Council on Bioethics, one could potentially remove the remaining one or two functioning blastomeres from this "dead" embryo, and further culture them *in vitro* to a stage from which hESCs can be isolated.[22] It is important to note that a dividing, totipotent blastomere is potentially equivalent to a living embryo. Therefore, this strategy may be no more ethically acceptable than the current method of deriving hESCs from a living embryo. However, if an IVF embryo is cultured further to the blastocyst stage and subsequently ceases coordinated division, it is possible that some of the inner cells—which may still be dividing but are not totipotent—may be isolated to derive hESC lines.

Embryos that have ceased coordinated division are organismically dead and are frequently genetically abnormal: many contain abnormal numbers or sets of chromosomes (DNA-protein structures). From a therapeutic point of view, hESC lines derived from genetically deranged embryos may not be pluripotent. Alternatively, they may be otherwise undesirable for clinical use because of a propensity to form tumors or an inability to differentiate properly or survive. However, abnormalities that cause specific diseases, such as certain cancers and Down syndrome, may be useful to researchers who study the genetic pathways underlying such disorders.

B. "Living" Embryos Intended for Implantation

Extraction of blastomeres from a "living" embryo is already performed through a clinical procedure known as preimplantation genetic diagnosis (PGD). PGD is generally undertaken in conjunction with IVF techniques in order to test for specific genetic abnormalities of the embryo prior to uterine transfer. PGD is conducted during the 2-8 cell stage when the embryo is made up of equivalent, totipotent blastomeres. Interestingly, at this stage, the embryo can compensate for the loss of a blastomere and remain viable for full-term development.[23] One or two blastomeres from several IVF-generated early embryos are removed and tested for a genetic disease. At this early stage, extraction of a single blastomere is equivalent to "twinning" the embryo, because the cell to be biopsied, now separate from the original embryo, may have the potential to develop full-term if implanted into the uterus.

It is conceivable that an additional blastomere may be removed during PGD to derive ESC lines. In 2006, two studies by Lanza and colleagues reported the

22. PRESIDENT'S COUNCIL ON BIOETHICS, ALTERNATIVE SOURCES OF HUMAN PLURIPOTENT STEM CELLS 8, 9 (2005), *available at* http://www.bioethics.gov/reports/white_paper/alternative_sources_white_paper.pdf.

23. *See id.* at 24-25.

generation of ESC lines from murine and human single cell blastomeres.[24] In the murine study, single blastomeres were extracted from developing embryos to derive ESC lines; some of the remaining biopsied embryos, if implanted, could develop into viable mice. In the human study, some ninety-one single cells were extracted from sixteen spare IVF embryos, and two hESC lines were derived.

There are several caveats to the human study. First, cell extraction may delay implantation of the embryo, which can endanger its development. Lanza and colleagues note that in PGD, a single blastomere is taken from the embryo. In their study, multiple blastomeres were taken from single embryos and blastomeres from the same embryos were cultured together; the biopsied human embryos were destroyed without implantation. If this procedure were adapted for clinical use, the authors envision that a single blastomere would be removed and allowed to divide in culture, so that separate cells derived from a single blastomere could be used for PGD and for the generation of hESCs. (The alternative, extracting more than one blastomere from the human embryo, likely presents unacceptable risks for the viability of the biopsied embryo.) If only one blastomere were removed, it would be necessary to delay the transfer of the embryo into the uterus until the extracted blastomere divided sufficiently to permit cell extraction for both PGD and hESC derivation. This delay may compromise the success of subsequent embryo transfer and embryonic development due to perturbation of parental imprinting (an epigenetic state dependent on proper expression of maternal and paternal genes). Second, instead of culturing multiple blastomeres from the same embryo (which fosters cell-to-cell contact and may improve *in vitro* proliferation, survival and development), Lanza et al. propose that the extracted blastomere and biopsied embryo should be cultured together *in vitro*. This practice would again prolong the time the embryo would be in culture before uterine transfer. Despite these limitations, these studies offer an interesting alternative to research cloning by allowing the generation of genetically matched hESC lines for some children.

While these alternatives to research cloning may be potentially helpful for future cell therapy of children conceived via IVF and PGD, the long term risks of this method of blastomere extraction are currently unknown. Removal of an additional blastomere for derivation of a hESC line may present further risks. Finally, if a hESC line is generated from a "normal" blastomere, the derivation of hESC lines would necessarily involve the destruction of a "twinned" embryo equivalent: the totipotent blastomere, which would not develop into a child. This approach would not avoid the ethical concerns discussed above. A blastomere with severe genetic aberrations such that the resulting embryo from which the blastomere was extracted could *not* develop to full term, could be a valuable

24. Young Chung et al., *Embryonic and Extraembryonic Stem Cell Lines Derived from Single Mouse Blastomeres*, 439 NATURE 216 (2006); Irina Klimanskaya et al., *Human Embryonic Stem Cell Lines Derived from Single Blastomeres*, 444 NATURE 481 (2006).

source of hESCs used for studying genetic diseases. However, it is not obvious that such genetic abnormalities can be identified during PGD.

In short, extraction of a dividing, totipotent blastomere from an organismically dead embryo or one from a living embryo intended for uterine transfer does not avoid the destruction of an embryo equivalent.

C. Altered Nuclear Transfer Resulting in Biological Artifacts

Another approach, called altered nuclear transfer (ANT), advanced by William Hulburt, a member of the President's Council on Bioethics, posits that inactivation of specific genes required for full viability but *not* for generation of ESCs would result in a "biological artifact" from which pluripotent cells could be derived.[25] Since, like a parthenote, the "biological artifact" cannot develop into an embryo, some may view this as a more ethically acceptable source of hESCs than derivation of cells from a potentially viable fertilized or cloned embryo. In both ANT and the derivation of cells from a potentially viable embryo, the somatic nuclei may further be altered, such as to represent a specific genetic disorder, and the hESC lines derived from them could then be used to study pathogenesis of a genetic disease and evaluate new drugs to treat such a disorder.

Indeed, an elegant study has validated the feasibility of this approach through conditional inactivation of the gene *Cdx2* in mouse embryonic stem cells. *Cdx2* is essential for generation of extra-embryonic tissue called trophoectoderm, which is the outer cell layer of the embryo that implants into the placental wall.[26] Conditional repression of C*dx2* rendered mouse embryos unable to implant, but the embryos still generate ESCs. The gene can then be subsequently reactivated, allowing differentiation into intestinal cells, whose specification also requires C*dx2* expression.

As the *Cdx2* study demonstrates, there remain several concerns in translating ANT processes to humans. *Cdx2* may be expressed differently in humans than in mice, and so it remains a possibility that *Cdx2*-inactivated human embryos may still have the ability to implant. Moreover, conditional inactivation was achieved by transfer of a retroviral vector which, if integrated in the vicinity of a cancer-growth gene (oncogene), may initiate tumorigenesis. While this work represents an important proof-of-principle demonstration of ANT, conditional activation of a gene required for placental implantation would render an otherwise healthy embryo into an abnormal one; in essence, it would create a genetically hobbled embryo. Therefore, ANT remains ethically problematic.[27]

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25. *See* PRESIDENT'S COUNCIL ON BIOETHICS, *supra* note 22, at 36-37.

26. Alexander Meissner & Rudolph Jaenisch, *Generation of Nuclear Transfer-Derived Pluripotent ES Cells from Cloned* Cdx2*-Deficient Blastocysts*, 439 NATURE 212 (2006).

27. Lawrence Masek, *A Contralife Argument Against Altered Nuclear Transfer*, 6 NAT'L CATH. BIOETHICS Q. 235 (2006).

In order to use ANT and other "reprogramming" techniques to derive hESC or human iPS lines without creating or destroying the embryo, a deeper understanding of mechanisms of reprogramming and regulation of the epigenetic state will be essential. Additional research will be necessary to use these cells in human therapy. Ideally, cells would be stably reprogrammed to the desired fate by expression of particular genes, *in vitro*, and then be used for clinical therapy. However and it is unclear whether human parthenotes would be considered an ethically acceptable source of hESC lines. Alternatives to ANT, such as cell fusion-dependent processes of dedifferentiation and transdifferentiation, may not be desirable because fusion is a rare event; even if fusion is successful, the resulting cells contain two nuclei, although the expulsion of the extra nucleus may be a temporary technical obstacle. Another alternative, fusion-*independent* transdifferentiation of cells following transplantation is still largely unexplored. Molecules such as 5-azacytidine and other DNA methylation- and histone acetylation-modifying molecules have proven useful in combating leukemia by "reprogramming" cancer cells to express cellular death genes;[28] however, these molecules are also toxic. A promising study, discussed below, by Yamanaka and colleagues demonstrates that reprogramming may be possible via expression of relatively few specific genes; however, more research is needed.[29]

IV. IMMUNOLOGIC ACCEPTANCE AND REJECTION

As an alternative to generating new hESC lines, recent research suggests that it may be possible to manipulate the genes that mediate the immune response in order to generate immune-compatible tissue derived from existing approved stem cell lines. The generation of immunologically compatible, autologous tissues from hESC lines remains the primary advantage of research cloning. The generation of hESCs through a non-cloning procedure, such as using embryos created through *in vitro* fertilization, does not produce genetically-matched cells. As a result, transplantation would require the patient to endure a regimen of immunosuppressive drugs. Besides the known danger of tumor formation, recent evidence has suggested that transplantation of allogeneic (non-immune-compatible) undifferentiated hESCs may also result in rejection because undifferentiated hESCs express low levels of immunogenic molecules.[30] Even if appropriately differentiated allogeneic hESCs are transplanted, the required immunosuppressive drugs may give rise to many adverse effects, including

28. *See, e.g.*, G. Zardo, G. Cimino & C. Nervi, *Epigenetic Plasticity of Chromatin in Embryonic and Hematopoietic Stem/Progenitor Cells: Therapeutic Potential of Cell Reprogramming*, 22 LEUKEMIA 1503, 1512 (2008).

29. Takahashi & Yamanaka, *supra* note 1.

30. Micha Drukker et al., *Characterization of the Expression of MHC Proteins in Human Embryonic Stem Cells*, 99 PROC. NAT'L ACAD. SCI. 9864 (2002).

increased risks for cancer and infection. Autologous tissues derived from hESCs produced through research cloning, which elicit little or no immune reaction, offer a superior avenue for therapy, although the potential for tumor formation from undifferentiated cells remains.

Although research cloning remains contentious, scientists may already be able to exploit the therapeutic advantages of well-studied, non-autologous hESC lines (such as those derived from supernumerary embryos from IVF clinics). A study at Stanford University in 2002 demonstrated that small numbers of kidney transplant recipients who are irradiated and then given bone marrow stem cells isolated from the original kidney donor can be successfully weaned from immunosuppressive drugs.[31] This is because the donor bone marrow stem cells reconstitute the irradiated recipient's blood and immune system, resulting in the development of donor-derived immune cells that do not reject the donor kidney.

An added advantage of this method is that the donor need not be immunologically compatible—the recipient would not necessarily have to rely on donors who have a similar immune type (such as siblings). Using this method, future tissues developed from well-studied but immunologically-mismatched hESC lines—such as the ones currently available—can be transplanted with decreased risk of immune rejection and ultimately be weaned from harsh immunosuppressive regimens. For example, following a severe heart attack, injection of cardiomyocytes derived from allogeneic hESCs into the area of infarction may offer future therapy to improve function and overall survival. In this case, following grafting of the cardiomyocytes, the patient would undergo immunosuppressive therapy to reduce the risk of immediate rejection. Following stabilization, the patient may be irradiated and then given hematopoietic stem cells derived from the same line of hESCs that generated the grafted cardiomyocytes. Transplanted hematopoietic stem cells would engraft and generate immune cells that tolerate the graft because the cells would be isogenic (of the same genotype) to the cardiomyocyte graft. Gradually, the patient would be weaned off the immunosuppressive drugs and would avoid long-term adverse effects.

However, irradiation and bone marrow stem cell transplantation carry very serious risks, including a high proportion of life-threatening infections and rejection of the hematopoietic stem cell transplant. Whether induction of immune tolerance to the graft through this method or generation of autologous tissues through research cloning on a per-patient-basis will provide the preferred method will depend on the life-threatening risk of the former versus the expense of the latter. However, the recent, comparably facile, derivation of several iPS cell lines offers an alternative method by which immune-matched cell grafts can more

31. Maria T. Millan et al., *Mixed Chimerism and Immunosuppressive Drug Withdrawal After HLA-Mismatched Kidney and Hematopoietic Progenitor Transplantation*, 73 TRANSPLANTATION 1386 (2002).

safely and economically be used for therapy. This method would offer substantially lower life-threatening risks than combined irradiation and bone marrow transplantation to induce immune tolerance of grafted tissues from allogeneic hESC lines.

A. Overcoming Immune Rejection

Genetic modification of determinant genes that mediate immune response, parthenogenesis, and the transfer or addition of other cell-free extracts that contain the molecular factors capable of reprogramming the differentiated cell may offer alternative means to generate stem cell-derived, immune-compatible tissue. The *major histocompatibility complex* (MHC) refers to the cell surface proteins that determine whether the cell will be accepted or rejected by the immune system. Through a genetic manipulation called homologous recombination, MHC proteins may be modified or deleted such that the altered cells do not provoke an immune response in the recipient following transplantation. It would seem that this is not without new problems.

Female patients who donate the eggs from which parthenogenetic hESCs are generated may be able to receive tissue transplants derived from these cells without immune rejection. This is because parthenogenetic cells are largely endowed with the same genetic information as the female host. Still, prior recombination of MHC genes in meiosis (specialized division of the egg) may produce parthenogenetic tissue derivatives not immunologically matched to the host, resulting in a mild degree of immune rejection.

The addition of foreign mitochondrial DNA present in the transplanted donor ooplasm via ooplasmic transfer[32] may also trigger some degree of immune rejection.[33] Transplantation of cell extracts (rather than whole ooplasm) that reprogram the host cell into therapeutic cell types may circumvent this risk.

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32. *See infra* Section V.B.

33. *See, e.g.*, Vanessa J. Hall, Petra Stojkovic & Miodrag Stojkovic, *Using Therapeutic Cloning to Fight Human Disease: A Conundrum or Reality?*, 24 STEM CELLS 1628, 1633 (2006) ("It should be considered that allogeneic mitochondria present in NT-ESC or NT-ESC derived cells could be recognized by the host immune system, leading to disrupted mitochondrial membrane potential that induces the apoptotic cell signaling pathway, thus leading to cell death."); Charlotte Kfoury, *Therapeutic Cloning: Promises and Issues*, 10 MCGILL J. MED. 112, 116-117 (2007) ("Immune rejection of the ntESC in cell replacement therapy is due to mitochondrial heteroplasmy as a consequence of SCNT since the nuclear donor and ooplasmic host cells are not autologous in most cases . . . . Also, antigens such as Mta are encoded by the mitochondrial genome and trigger an auto-immune response targeting the hybrid (36) after transplantation."); Robert P. Lanza, Jose B. Cibelli & Michael D. West, *Prospects for the Use of Nuclear Transfer in Human Transplantation*, 17 NATURE BIOTECHNOLOGY 1171, 1173 (1999) ("The mitochondrial genome of vertebrates is extremely specialized, and incompatibilities are likely between distantly related species.").

Nonetheless, without elucidation of the molecular factors capable of reprogramming and the mechanism by which it takes place, it is unknown whether tissues derived through this procedure would elicit immune rejection.

V. REPROGRAMMING: DEDIFFERENTIATION AND TRANSDIFFERENTIATION

Finally, the most scientifically promising techniques for pursuing hESC alternatives are dedifferentiation and transdifferentiation, both of which involve reprogramming specialized cells.

A. Dedifferentiation: Fertilization and Parthenogenesis

Dedifferentiation is a specific type of reprogramming in which a specialized cell reverts to a more primitive state, such as a progenitor or stem cell. Both *fertilization* and *parthenogenesis* result in the reprogramming and dedifferentiation of a differentiated egg cell into primitive and other differentiated cells. Fertilization is the predominant means of reprogramming—and reproduction—among mammalian species. The generation of hESC lines from embryos generated via fertilization of donated human eggs and sperm requires the creation and destruction of an embryo. It is also less therapeutically attractive because such lines would not be genetically matched to any patient. Germ cells (eggs and sperm) have been generated from mouse ESCs.[34] *In vitro* generation of germ cells, especially eggs, from existing hESC lines would obviate the need for donation of germ cells from human volunteers for generation of new hESC lines. However, induced pluripotent stem cell reprogramming (see below) or research cloning would still be necessary to produce genetically compatible tissue.

Parthenogenesis is the process of development of an unfertilized egg into viable offspring. In general, this process does not occur in mammalian species, but it occurs in other types of animals such as reptiles and insects. Through chemical manipulation, mouse and monkey parthenogenetic blastocysts can develop *in vitro*, from which pluripotent ESCs can be harvested.[35] These ESCs have a full complement of DNA, can be extensively propagated, can differentiate into most if not all cell types, and can engraft following transplantation.[36] Recently, unfertilized oocytes coaxed to the blastocyst stage have been used to

34. Neils Geijsen et al., *Derivation of Embryonic Germ Cells and Male Gametes from Embryonic Stem Cells*, 427 NATURE 148 (2004); Karin Hubner et al., *Derivation of Oocytes from Mouse Embryonic Stem Cells*, 300 SCIENCE 1251 (2003).

35. Jose B. Cibelli et al., *Parthenogenetic Stem Cells in Nonhuman Primates*, 295 SCIENCE 819 (2002).

36. Rosario Sanchez-Pernaute et al., *Long-Term Survival of Dopamine Neurons Derived from Parthenogenetic Primate Embryonic Stem Cells (Cyno-1) After Transplantation*, 23 STEM CELLS 914 (2005).

generate parthenogenetic hESC lines, just as parthenogenetic monkey ESCs were derived in 2002.[37] Parthenogenetic human embryos are unlikely to be viable; parthenogenetic rodent embryos are not viable unless the methylation of certain genes is modified in the laboratory.[38] For this reason, some may consider these as more ethically acceptable sources for generating hESC lines than potentially viable fertilized eggs and cloned embryos. An interesting consequence of this method is that parthenogenetic ESCs would, in theory, be immunologically matched only to those females who donate the eggs from which the cells were derived. Recently, parthenogenetic hESC lines were generated from oocytes of women representing different immunologic groups, which might be a step toward generating immunologically compatible parthenogenetic tissues.[39]

B. Dedifferentiation with Cell-Free Extracts: Nuclear and Cytoplasmic Transfer

In somatic cell nuclear transfer (SCNT), an adult nucleus from a differentiated cell is reprogrammed to a primitive state, recapitulating embryonic development, from which pluripotent ESCs or even viable, entire organisms can be derived. In one experiment, a nucleus from a differentiated human immune cell was transferred into a frog egg. Nuclear and cytoplasmic factors from the frog egg reprogrammed the adult human nucleus to express a primitive hESC protein while extinguishing the expression of differentiated genes, suggesting that it may be possible to dedifferentiate the differentiated human nucleus into a pluripotent-like state.[40] While it has been considered that the nucleus of an immature, undifferentiated cell (e.g., an ESC) is more efficient than that of a mature cell that has ceased dividing, recent evidence has suggested the opposite.[41] Nuclei from a type of differentiated immune cell, a postmitotic granulocyte, have proven to be much more efficient donors for SCNT than nuclei from hematopoietic stem cells (from which granulocytes are derived). This is a positive development for research cloning; differentiated cells from the blood and immune system, skin, and other organs are, in general much more accessible (and more common) than immature cells such as stem cells, which are often rare or inaccessible for isolation from adult tissues.

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37. Elena S. Revazova et al., *Patient-Specific Stem Cell Lines Derived from Human Parthenogenetic Blastocysts*, 9 CLONING STEM CELLS 432 (2007).

38. David A. Loebel & P.P. Tam, *Genomic Imprinting: Mice Without a Father*, 428 NATURE 809 (2004).

39. Elena S. Revazova et al., *HLA Homozygous Stem Cell Lines Derived from Human Parthenogenetic Blastocysts*, 10 CLONING STEM CELLS 11 (2008).

40. James A. Byrne et al., *Nuclei of Adult Mammalian Somatic Cells Are Directly Reprogrammed to* Oct-4 *Stem Cell Gene Expression by Amphibian Oocytes*, 13 CURRENT BIOLOGY 1206 (2003).

41. Li-Ying Sung et al., *Differentiated Cells Are More Efficient than Adult Stem Cells for Cloning by Somatic Cell Nuclear Transfer*, 38 NATURE GENETICS 1323 (2006).

Hitherto used exclusively as an experimental assisted reproductive technology, *ooplasmic transfer* involves the transfer of oocyte cytoplasm into another cell such as a damaged egg in order to repair defects in the recipient cell. The technique has resulted in the birth of over thirty children to mothers previously unable to conceive. Other *"zona-free" cloning techniques* effectively fuse ooplasm with a differentiated cell, which can also reprogram differentiated cells. Central to reprogramming methods, including SCNT, is the presence of reprogramming factors in the egg and ESC cytoplasm. These factors contain particular proteins that can alter the epigenetic state and patterns of gene expression in a cell, thereby reprogramming differentiated cells into a primitive state.

C. Dedifferentiation by Cell Fusion

In 2002, British researchers recognized that co-culture of fetal and adult central nervous system cells with ESCs resulted in fused cells that had properties of ESCs, including ESC-specific marker expression and multilineage differentiation following transplantation. The resulting fused cell contains two nuclei and cytoplasmic components from both cells. Apparently, the actual state of the fused cell resembles the more primitive ESC, rather than the differentiated cells, suggesting that the factors in the ESC nucleus and cytoplasm are dominant to those of the differentiated cells.[42]

In 2005, U.S. researchers described the derivation of ES-like cells from the fusion of human ESCs with human somatic fibroblasts.[43] These hybrid cells display properties of ESCs including extensive self-renewal, reactivation of the pluripotent-specific gene *Oct4* (by demethylation of the promoter in the fibroblast genome), and differentiation into a variety of cell types. The fusion event takes place, however, at an extremely low frequency. Moreover, the resulting fused cell contains two sets of DNA, and the ESC nucleus must be expelled. Should removal of the hESC nucleus from the fused cell be possible, the generation of patient-matched ES-like cells through a cell fusion process that does not involve the creation of an embryo may be feasible.

D. "Transdifferentation": Cell Fusion, Cell-Free Extracts, and Epigenetic Modifiers

Transdifferentiation, another specialized form of reprogramming, refers to the process by which a cell derived from one germ layer converts to a cell from another germ layer. Early in embryonic development, cell types are segregated into three major germ layers: the ectoderm (which generates the skin and CNS),

42. Qi-Long Ying et al., *Changing Potency by Spontaneous Fusion*, 416 NATURE 545 (2002).

43. Chad Cowan et al., *Nuclear Reprogramming of Somatic Cells After Fusion with Human Embryonic Stem Cells*, 309 SCIENCE 1369 (2005).

the mesoderm (which generates blood, muscle and bone), and the endoderm (which generates the respiratory and gut lining, liver and other structures). Once the germ layers are established, it is thought that a cell derived from one germ layer cannot readily convert into a cell from another germ layer.

Some early reports described the conversion of "blood into brain," that is, the conversion of bone marrow cells (mesoderm) into neural cells (ectoderm) following transplantation of bone marrow.[44] Closer inspection of such cells revealed that they harbored two nuclei and were a result of cell fusion.[45] However, other experiments have since been conducted, revealing for example, that transplanted bone marrow cells could indeed "transdifferentiate" into the cells that comprise the lining of the lung (endoderm) through a fusion-independent mechanism.[46] However, these events occurred at too low a frequency to be considered therapeutically beneficial. Despite a report demonstrating extensive bone marrow cell contribution to stomach tumors (an endodermal cancer),[47] it is unclear whether such transdifferentiation can robustly generate dividing, clinically useful cells for therapy of disease in which specific cell types are lost.

Additional experiments have shown that other cell-free extracts, such as cytoplasm of immune system cells, contain reprogramming factors and are sufficient to convert a differentiated cell type into another differentiated-like cell.[48] Specific molecules that alter DNA methylation and histone acetylation can activate specific cell-type genes to reprogram cells. One agent, 5-azacytidine, demethylates specific portions of DNA, allowing reexpression of specific genes, including those crucial to cell type identity. In one study, following 5-azacytidine treatment, neural stem cells that normally give rise to only neural lineages generated contractile cardiomyocytes.[49]

E. The "Grail": The Derivation of iPS cells and Direct Transdifferentiation

Since a unique pattern of gene expression defines cell identity, manipulation of specific genes and epigenetic factors may enable dedifferentiation,

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44. Timothy R. Brazelton et al., *From Marrow to Brain: Expression of Neuronal Phenotypes in Adult Mice*, 290 SCIENCE 1775 (2000).

45. James M. Weimann et al., *Stable Reprogrammed Heterokaryons Form Spontaneously in Purkinje Neurons After Bone Marrow Transplant*, 5 NATURE CELL BIOLOGY 959 (2003).

46. Robert G. Harris et al., *Lack of a Fusion Requirement for Development of Bone Marrow-Derived Epithelia*, 305 SCIENCE 90 (2004).

47. JeanMarie Houghton et al., *Gastric Cancer Originating from Bone Marrow-Derived Cells*, 306 SCIENCE 1568 (2004).

48. Anne-Mari Hakelien et al., *Reprogramming Fibroblasts To Express T-Cell Functions Using Cell Extracts*, 20 NATURE BIOTECHNOLOGY 460 (2002).

49. Mahmud Bani-Yaghoub et al., *Insulin Acts as a Myogenic Differentiation Signal for Neural Stem Cells with Multilineage Differentiation Potential*, 131 DEVELOPMENT 4287 (2004).

transdifferentiation, and other types of reprogramming. Insights from animals engineered to lack or overexpress certain genes have offered clues as to which genes are crucial to cell type specification. There are several methods to modify gene expression; while the technical details are beyond the scope of this discussion, the approach is to either decrease or increase expression of specific genes, such as the transcription factors discussed above, in order to reprogram the cell to a desired state.

Researchers have envisaged genetic strategies to dedifferentiate somatic cells to pluripotent cells, without the generation of a totipotent embryo as a necessary intermediate—the so-called "grail" of therapeutic stem cell biology. In a landmark study published in 2006, Japanese researchers devised a method to enable this type of reprogramming, which they called "induced pluripotent stem cell" (iPS) reprogramming.[50] By introducing genes known to be expressed in stem, progenitor, and dividing cells, Yamanaka and colleagues, in a combinatorial fashion, deduced which genes could reprogram differentiated murine fibroblasts into ES-like cells. Forced expression of as few as four genes, *Oct4, Sox2, c-Myc,* and *Klf4*, reprogrammed adult cells into ES-like cells. Such cells which could be propagated extensively, expressed several ESC marker genes, differentiated into a variety of tissues, and contributed to mouse embryonic development. Interestingly, while the reprogrammed ES-like cells more resembled bona fide ESCs than the parental fibroblasts, they displayed a gene expression pattern distinct from either. Indeed, the DNA methylation state of pluripotent-specific gene *Oct4* in the reprogrammed ES-like cells resembled an intermediate between ESCs and fibroblasts. By identifying the genes capable of reprogramming a differentiated somatic cell, Yamanaka and colleagues offer some of the first evidence that pluripotent cells can indeed be derived from differentiated cells without the creation of an embryo.

Since the publication of this seminal paper, a flurry of reports have confirmed and extended these observations. iPS cells have since been derived from human somatic cells by Yamanaka's team using the same factors as with mice, while another American team has used a slightly different combination of transcription factors to achieve a similar result.[51] Adult neural, stomach, and liver cells have been reprogrammed to iPS cells.[52] By treating mouse and human fibroblast cells with epigenetic modifiers (agents that modulate DNA and histones by promoting or inhibiting methylation and acetylation), successful conversion to iPS cells can be achieved without ectopic expression of oncogenes,

50. Takahashi & Yamanaka, *supra* note 1.

51. Takahashi et al., *supra* note 1; Jungying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917 (2007).

52. Aoi et al., *supra* note 1; Jeong Beom Kim et al., *Pluripotent Stem Cells Induced from Adult Neural Stem Cells by Reprogramming with Two Factors*, 454 NATURE 646 (2008).

such as *c-Myc* or *Klf4*.[53] Recently, Yamanaka and colleagues have demonstrated that transfection (a technique whereby a virus encoding an oncogene like *c-Myc* does not permanently integrate into the cell genome) of fibroblasts can yield iPS cells.[54] The stage is set whereby transient application of reprogramming factors, such as cytokines that induce expression of specific transcription factors or chemical epigenetic modifying agents, can be used to convert easily isolable adult cells to iPS cells without prolonged expression of tumorigenic genes.

The use of murine and human iPS derivatives for therapy in animal models, along with our increased understanding of the susceptibility of certain cell types to environmental insults, hints at future applications of iPS technology. A recent study reprogrammed skin from mice with the sickle cell anemia mutation. The skin from these mice was reprogrammed into iPS cells using *Oct4, Sox2, Klf4* and *c-Myc*, as above. The resulting iPS cells were then electroporated with the normal hemoglobin gene, pushed toward the hematopoietic lineage, and autologously transplanted into the sickle cell mice. The transplanted cells engrafted and reconstituted the blood system and improved red cell morphology, mass, and urine concentration defects (also seen in human sickle cell patients).[55] Another report has derived patient-specific iPS cell lines from the skin of patients living with amyotrophic lateral sclerosis (ALS). Large numbers of motor neurons could be generated from these iPS cells, allowing the production of immune-matched cells for autologous transplantation as well as the study of pathophysiologic processes from crucial cells lost in specific diseases.[56]

In order to generate clinically useful cell types, is a "dedifferentiation" step actually required? That is, must one reprogram a differentiated cell to a "dedifferentiated" embryonic/iPS intermediate state before producing another differentiated cell type? As discussed in the "transdifferentiation" section, cell-free extracts and chemical inhibitors of DNA methylation have converted one differentiated cell type into another. However, it is difficult to know if a more primitive intermediate cell was generated.

A recent study has demonstrated direct reprogramming from one differentiated cell type to another *in vivo*.[57] Viruses encoding cell-type specific

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53. Danwei Huangfu et al., *Induction of Pluripotent Stem Cells from Primary Human Fibroblasts with Only* Oct4 *and* Sox2, 26 NATURE BIOTECHNOLOGY 1269 (2008); Yan Shi et al., *Induction of Pluripotent Stem Cells from Mouse Embryonic Fibroblasts by* Oct4 *and* Klf4 *with Small-Molecule Compounds*, 3 CELL STEM CELL 568 (2008).

54. Okita et al., *supra* note 1.

55. Jacob Hanna et al., *Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin*, 318 SCIENCE 1920 (2007).

56. John T. Dimos et al., *Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons*, 321 SCIENCE 1218 (2008).

57. Qiao Zhou et al., In Vivo *Reprogramming of Adult Pancreatic Exocrine Cells to Beta-Cells*, 455 NATURE 627 (2008).

transcription factors were injected into the adult mouse pancreas, and have been shown to convert pancreatic exocrine cells into pancreatic endocrine cells in the adult pancreas. While these two populations of cells are from the same germ layer (endoderm), they have separate metabolic functions and produce separate products. Amylase-producing exocrine cells, when forced to express *Ngn3, Pdx1*, and *Mafa*—three transcription factors important for development of endocrine pancreas—were induced into insulin-producing, endocrine cells *in vivo*. After injection of the virus, there was no increase in pancreatic cell division, suggesting that a dividing, stem-like intermediate cell is not required to achieve this conversion. Moreover, injection of the virus encoding the three transcription factors into diabetic mice demonstrated reduction in blood sugar levels.[58]

CONCLUSION

Research cloning and the cutting-edge "alternative" technologies discussed above exemplify the creativity of the researchers who push the boundaries of science and medicine in order to better understand the biological world and seek powerful new treatments for intractable diseases. Currently, most researchers still hope for expanded public funding of research using additional, newer embryonic stem cell lines, from both iPS cells and traditional sources. Despite formidable challenges, exciting progress has been made, most notably the derivation of iPS cells from easily isolable tissues such as adult fibroblasts and skin. The rapid pace of science and medicine suggests there may well be a day, sooner than the very distant future, when a simple skin biopsy will provide an unlimited number of immune-matched cells for any patient. Together, these studies have heralded the new era of stem cell biology. As a prominent stem cell biologist has concluded, "the controversial issues (ethical and technical) specific to human therapeutic [research] cloning may well be left behind along with the procedure itself, a refreshing change for the field, indeed."[59]

58. *Id.*

59. Jose Cibelli, *Is Therapeutic Cloning Dead?*, 318 SCIENCE 1879, 1879 (2007).