Stem Cell Research in the U.S. after the President's Speech of August 2001

CYNTHIA B. COHEN

On 9 August 2001, in a nationally televised speech, President Bush addressed the contentious question of whether to provide federal funds for human embryonic stem cell research (White House 2001).[1] This research involves taking the primordial cells found in embryos and transforming them into certain specialized cells, such as those of the heart, nerves, and muscles, with the ultimate goal of transferring these cells into patients to repair damaged cells and tissues. In his remarks, the President authorized funding for research only on stem cells already harvested from remaining embryos at *in vitro* fertilization (IVF) centers as of 9 August 2001, the date of the speech. In a "Fact Sheet" about embryonic stem cell research, he added the ethical requirements that (1) the donors of embryos gave informed consent to the derivation of stem cells from their embryos, (2) the embryos were created solely for reproductive purposes, and (3) no financial inducements were given to the embryo donors. The President also prohibited federally funded research on embryonic stem cells derived from embryos after 9 August 2001, as well as the creation of embryos for research purposes and the cloning of human embryos for both reproductive and research purposes. He did not seek to ban the pursuit of embryonic stem cell research with private funds. "This allows us to explore the promise and potential of stem-cell research without crossing a fundamental moral line by providing taxpayer funding that would sanction or encourage further destruction of embryos," the President stated (White House 2001).

The President's speech stirred intense controversy. Many applauded the new policy because it allowed some embryonic stem cell research to proceed, thereby raising hope that treatments might be developed for those suffering from such conditions as Parkinson's disease, Alzheimer's disease, and diabetes. Others supported it on grounds that it would discourage the future destruction of embryos in stem cell research. They maintained that although it was wrong to have derived stem cells from embryos, this wrong was no longer remediable and it therefore was justifiable to allow research using such embryos to proceed. Some, however, objected to the new policy because they held that it unduly limited the

Kennedy Institute of Ethics Journal Vol. 14, No. 1, 97–114 © 2004 by The Johns Hopkins University Press

number of embryonic stem cells available for federally funded research. Still others opposed it on grounds that it made the federal government complicit in what they took to be the wrongful destruction of human embryos that had taken place prior to 9 August 2001. The President established the President's Council on Bioethics by executive order in November 2001 and charged it, among other tasks, with monitoring stem cell research and recommending guidelines and regulations for biomedical innovations.

Questions about the moral status of human embryos have so captured public attention since the President issued his remarks that other significant ethical and policy issues raised about stem cell research inside the Beltway have remained in the shadows. A number of individuals and organizations—legislators, scientists, patient groups, the President's Council on Bioethics, ethicists, religious task forces, and social commentators—have attempted to bring these other issues to legislative and public attention. They also have revisited the more publicly prominent question of what sorts of protections we owe to human embryos. In response, Congress has attempted to address several of these newly emerging issues at hearings and in legislation. I review these efforts, consider developing issues and arguments, and conclude by exploring possible future directions for federal and private sector stem cell policy.

THE AVAILABILITY OF EMBRYONIC STEM CELL LINES TO FEDERALLY FUNDED RESEARCHERS

President Bush, in developing his stem cell research policy, accepted a distinction between the "derivation" and the "use" of embryos enunciated by the General Counsel of the Department of Health and Human Services toward the end of the Clinton administration. This distinction was adopted to avoid contravening the Dickey-Wicker Amendment (added to The Balanced Budget Downpayment Act. Public Law No. 104–99, Title I. Sec. 1996), which prohibits the destruction of human embryos in federally funded research. It enabled the Clinton administration to allow the use of public funds for research on stem cells after they had been derived from the inner cell mass of embryos by researchers who had used private or foreign government funds to do so. However, President Bush modified the Clinton policy to narrow the number of embryonic stem cell lines that could be used in federally funded stem cell research to those already derived before 9 p.m. EST on 9 August 2001. His stated objective was to avoid encouraging the future destruction of human embryos.

Scientists and legislators who were skeptical about the number and quality of embryonic stem cell lines available for research at the time of the President's speech have continued to question the adequacy of the approved lines before legislative and advisory bodies. They largely have framed the issue as one of beneficence, arguing that insufficient stem cell lines are available to pursue the research at a rapid pace and that this wrongly leaves those individuals with seri-

ous degenerative conditions in sickness and suffering. Stem cell scientists hold that it is necessary to study embryonic stem cells derived by a wider variety of techniques than is possible under President Bush's policy in order to gain a basic understanding of how these cells work. Moreover, they maintain that it is important to examine a large sample size with more varied DNA profiles than are found in the approved lines in order to take account of individual variation in genetic makeup. Finally, these scientists declare that what they take to be the unduly limited number of embryonic stem cell lines available for federally funded research puts the United States at a competitive disadvantage with other countries that support research on a broader range of embryonic stem cells.

In his speech, the President stated that some 60 stem cell lines meeting the conditions he had laid down were available for federally funded research. That number soon leapt to 78. However, toward the end of 2003, only 12 of the approved embryonic stem cell lines were accessible to recipients of federal research grants.[2] Four to six more were expected to become available, and at the end of December 2003 three more were said by NIH to be ready for use in research.[3] Several leading stem cell investigators have claimed that a minimum of 200 embryonic stem cell lines is needed to carry out such research effectively. In contrast, James Battey, the head of the NIH Stem Cell Task Force that oversees stem cell research, has maintained that the available stem cell lines are sufficient for several more years of research.[4]

The number of approved embryonic stem cell lines is more limited than originally stated because some were in a primitive stage of development in August 2001 and remain frozen and unusable today. Certain other lines are not readily available to American investigators because of their costs, intellectual property issues, problems negotiating agreements with their owners, and restrictions on their export by foreign governments. Still other lines have died out or may be infected.

A serious concern about contamination hovers over the embryonic stem cell lines currently available because they have been grown with mouse feeder cells in order to prevent their premature differentiation. These feeder cells might contain viruses dangerous to human beings. At a Senate committee hearing in May 2003, Senators Arlen Specter (R-PA) and Tom Harkin (D-IA) stated that they had been informed by the Secretary of Health and Human Services and NIH administrators that all approved stem cell lines were being grown with these feeders. They therefore contended that the number of available lines should be expanded to include some that had been grown without them. The senators argued that new lines from Johns Hopkins University and others they had learned about from Sweden and Singapore that had been grown with human feeder cells or various fluids should be added to those approved for federally funded embryonic stem cell research.

In response, Elias Zerhouni, director of NIH, announced, to the surprise of the committee in view of previous administration and NIH statements, that 16

of the approved embryonic stem cell lines that apparently had not yet been cultured would be grown with human feeder cells or fluids. Senator Harkin observed that readying these 16 lines would entail unnecessary duplication of research already carried out at Johns Hopkins and abroad and would take at least another year to complete. Both Senators Specter and Harkin indicated that they would seek legislation authorizing the use of a larger number of more varied stem cell lines in federally funded research. Congress, however, has shown no inclination to either strengthen or weaken the President's policy since the hearing.

More recently, a working group at Johns Hopkins University declared that it would be unethical to use NIH-approved human embryonic stem cell lines in human subjects because they have been nurtured with mouse feeder layers and bear the risk of cross species transfer of infectious agents (Dawson et al. 2003). This risk could be avoided, the working group opined, if new stem cell lines were created for clinical trials without the use of mouse feeders.

Battey of NIH stated in response that Food and Drug Administration (FDA) representatives had asserted that stem cell lines grown on human feeder cells are not necessarily safer for use in humans than those grown on mouse feeder layers, since they, too, could harbor pathogens (Battey 2004). In addition, he observed, living cellular products that were developed using *in vitro* culture with living animal cells are currently being used in clinical trials approved by the FDA, suggesting that animal cells can safely be used in humans in some circumstances. Contact with feeder cells would be one of many safety considerations that would be addressed before clinical application of stem cell technology would be allowed by the FDA, he maintained.

Scientists, in turn, have stated that in the case of human feeder layers, pathogens are already known because they have previously produced disease in humans, whereas in the case of mouse feeder layers, some viruses without apparent pathology in the animal host have produced severe disease when "jumping" to humans. Further, they maintain, at least some of the products produced *in vitro* using animal cells are materials such as vaccines rather than cells themselves, and these are amenable to filtration to remove the potential contaminating agent. This is not possible when the preparation in question is a cell (containing the virus within its body). Thus, the discussion of the problem of viral contamination of NIH-approved stem cell lines currently remains at an impasse.

Meanwhile, stem cell investigators are turning to private groups to assist them in the creation of a greater number of embryonic stem cell lines. At the end of 2003, Douglas Melton at Harvard University announced that he had developed 17 new human embryonic stem cell lines with support from the Juvenile Diabetes Association and the Howard Hughes Medical Institute (Cowan et al. 2004). This nearly doubled the worldwide supply of embryonic stem cells available for research. Melton stated that he would give these cell lines to a private tissue storage facility in Virginia and to the United Kingdom Stem Cell Bank. Those re-

searchers in the United States who wish to work with these new lines must use private, rather than federal, funds, since these lines do not meet the conditions set out by President Bush.

Although private support for embryonic stem cell research increased in the wake of the President's remarks, several scientists and legislators maintain that it has not approached the sums of money that NIH would otherwise have directed to embryonic stem cell research. Moreover, some stem cell scientists who are receiving private support are uncertain whether they will be able to continue embryonic stem cell research in their current locations because their states are entertaining laws that would ban such research. Their alternative is to move to states that seem likely to authorize embryonic stem cell research or that already have done so, such as California and New Jersey.[5]

ETHICAL ISSUES RAISED BY ALTERNATE SOURCES OF STEM CELL LINES

Several other kinds and sources of stem cells besides those derived, as of 9 August 2001, from embryos remaining at IVF clinics are being used or considered for use by scientists in the United States. Some, such as adult stem cells, can be investigated with both federal and private funds. Others, such as stem cell lines derived from embryos specifically created for research, can be studied only with private funds. Debate about some of the major ethical questions related to the use of several of these kinds of cells has been underway inside the Beltway ever since the President announced his policy, but many of these questions have remained in the shadows outside the Beltway.

Germ Cells

Stem cells derived from the germinal ridge of already aborted fetuses are believed to be capable of generating many human cell types and are also capable of self-renewal. Research on these sorts of cells is approved for federal funding and is governed by federal guidelines. However, stem cell investigators, including those working with these germ cells, have maintained before Congress and the President's Council on Bioethics that embryonic stem cells hold greater promise of being able to differentiate into a wide range of different types of cells and tissue.

Adult Stem Cells

Some researchers have indicated that adult stem cells, such as those in bone marrow, blood, body fat, and certain organs, may provide an alternative to the use of embryonic stem cells. Recent studies have suggested that adult stem cells exhibit plasticity, the capacity to be brought to an unspecialized state and then differentiated into various cells of the human body. Investigators have concluded, for instance, that adult human bone marrow cells can be transformed into new liver, heart, and brain cells. This work has stimulated great excitement on the

Hill and has led some commentators to declare to congressional committees and the President's Council on Bioethics that the exclusive use of adult stem cells in research would avoid the daunting ethical questions raised by the use of embryonic stem cell lines.

The plasticity of some adult stem cells, however, has been brought into question recently. Toward the end of 2003, a study in *Nature* suggested that earlier bone marrow studies that had been taken to display the plasticity of adult stem cells had been incorrectly interpreted (Alvarez-Dolado 2003). The authors of this study found that adult bone marrow cells tend to fuse with available brain, heart, and liver cells, creating hybrid cells that give the appearance of having transformed into other types of cells when they have not. Other studies of adult blood and neural stem cells by investigators who were attempting to replicate earlier research that had been said to exhibit the plasticity of adult stem cells could not reproduce these previous results. Scientists specializing in adult stem cell research have stated that these divergent findings support the continuation of research with both embryonic and adult stem cells, rather than the abandonment of either.

Embryonic Stem Cells Created Through In Vitro Fertilization Solely for Research

Some legislators and their scientific advisors have urged Congress to lift President Bush's prohibition of the creation of embryos for research, arguing that this would boost the number of embryonic stem cell lines available. They have cited a 2002 study conducted by the Society of Assisted Reproductive Technology and the Rand Corporation in support of their claim that there are not enough frozen embryos remaining at IVF clinics to sustain future stem cell research. That study found that at least 396,526 embryos were in frozen storage in the United States (Hoffman 2003). Of these, 2.8 percent, or 11,000 embryos, were designated for research. However, only 275 of these embryos were deemed suitable for stem cell research because some had been damaged by freezing and others that had not been considered morphologically adequate for infertility treatment were also considered unusable in stem cell research. Therefore, these legislators maintain that embryos need to be created *de novo*.

One argument of those in Congress who object to the production of embryos for research is that to create embryos only to destroy them shows lack of respect for the embryos. Among the arguments of those who would allow such research is that the derivation of stem cells from embryos occurs well before the 14-day point at which early embryos individuate into single potential human beings and therefore to destroy them in research shows no disrespect to any potential human individual. Another counterargument heard in the halls of Congress is that until an embryo is transferred to the uterus, it is not a potential human being and it is therefore not wrong to create embryos for this research.

A second objection to the creation of embryos for stem cell research is that the practice would require the use of large numbers of human eggs from many women, thereby subjecting them to the known health risks of providing eggs. Moreover, the financial inducements currently used to attract women to provide eggs for research in the private sector, these objectors also argue, constitute a form of undue pressure. Groups that have produced embryos for research with private funding have responded that they obtain eggs only from women who have given informed consent, knowing the risks, and that they do not pay exorbitant amounts to induce them to provide eggs for research.

It seems highly unlikely that Congress would authorize the creation of new human embryonic stem cell lines with the use of federal funds in the near future. Privately funded investigators, however, are not legally prohibited from pursuing such research.

Embryonic Stem Cells Created Through Research Cloning

Because transplanted embryonic stem cells might be rejected by patients' immune systems, some scientists and legislators have proposed deriving stem cells from embryos created through a procedure variously known as "research cloning," "therapeutic cloning," or "somatic cell nuclear transfer." In it, the nucleus of an egg is removed and replaced by the nucleus of a somatic (body) cell from the patient. This egg is then stimulated chemically or electrically to develop into an embryo, stem cells are removed from its inner cell mass at the blastocyst stage, and these cells are transplanted into the patient. In February 2004, stem cell investigators in South Korea announced that they had created the first documented cloned human embryos and had derived a colony of stem cells from one of these embryos at the blastocyst stage (Hwang et al. 2004). They stated that they planned to use these stem cells to develop medical treatments to overcome the problem of rejection by the immune system of patients. The use of research cloning, its advocates maintain, would resolve the problem of graft versus host disease because these cloned stem cells would be genetically and immunologically compatible with their recipients. The Dickey-Wicker Amendment, however, prohibits the use of federal funding for research on embryos created by means of cloning in the United States.

The President's Council on Bioethics in 2002 endorsed a congressionally-enacted four-year moratorium on research cloning, maintaining that more time was needed to discuss the scientific and ethical merits of this procedure. The National Academy of Sciences, in contrast, issued a report in 2002 supporting the use of research cloning to prevent the immune rejection of stem cells and tissues derived from them.

Several bills introduced into Congress also have taken opposing approaches to the use of research cloning in stem cell research. One bill supported by the Bush administration and passed by the House of Representatives, but not the

Senate, in 2003 would have criminalized both reproductive and research cloning. Its authors maintained that all human cloning is essentially reproductive because there is no way to guarantee that research cloning would never be used for reproductive purposes. If unscrupulous scientists were to divert embryos cloned for research to the uteruses of women in order to create children, there would be no way to remedy this without resorting to abortion. It is wrong to create nascent human life by means of cloning, they argued, and even worse to destroy that life once created. It is therefore prudent not to engage in any form of cloning at all, they argued.

The other major stem cell research bill also would have made it a crime to engage in human reproductive cloning but would have allowed the pursuit of research cloning. The main arguments put forth in favor of this bill were that the embryos would develop and then be used only within the acceptable 14-day period cited above and that the bills would permit research within the United States, rather than overseas, that could be of great benefit to individuals with serious degenerative conditions. Proponents also contended that it was politically counterproductive to insist that both reproductive and research cloning be banned, for linking the two would mean that no bill would be passed, and thus reproductive cloning, which generally is agreed to be unacceptable, would not be prohibited nationally. Neither bill was passed by the Senate, and it is expected that both will be carried over to the 109th Congress of 2004.

Meanwhile, scientists have proposed other ways to address the problem of immune incompatibility. Some maintain that the creation of universal stem cell donor lines, in which genes have been altered or replaced to make them compatible with those of many patients, provides a way to resolve the problem of rejection without research cloning. Still other scientists, however, maintain that research cloning is the technique that can work most effectively to overcome this problem.

Embryonic Stem Cells Created Through Parthenogenesis

A few investigators using private sector funding have created embryos from human eggs through a process known as parthenogenesis. In it, chemicals are used to stimulate eggs to develop into embryos, whereupon these embryos divide until they form blastocysts from whose inner cell mass stem cells can be extracted. These embryos die within a few days, however, because they are haploid—i.e., have half the number of chromosomes in fertilized eggs—which causes the process of imprinting to go awry. Thus, it is doubtful whether they ever could develop beyond the early embryonic stages.

Some scientists working in this area maintain that since no viable human embryos are created by parthenogenesis, this procedure bypasses ethical objections to the use of human embryos in stem cell research. Other commentators, how-

ever, maintain that these embryos are no different from those created by IVF or research cloning and that a vocabulary change does not change the ethical issues involved. Moreover, several stem cell scientists indicate that stem cells derived from parthenotes would have very low use because of the difficulty of recovering stem cells from women in a short window and because it is unclear how functional these parthenotes would be.

The Dickey-Wicker Amendment includes in its definition of "embryo" any organism derived by parthenogenesis. Therefore, federal funding is not available for research in which parthenotes would be destroyed.

Embryonic Stem Cells Created Using Gametes Derived from Embryonic Stem Cells

The discovery in 2003 that mouse embryonic stem cells could transform themselves into egg cells spawned speculation on the Hill that human embryonic stem cells could some day be used to create embryos from which additional stem cells could be derived for research. It also raised the specter that such stem cells could be used to create children in the laboratory and to facilitate human genetic engineering. These concerns were reinforced when scientists found toward the end of 2003 that sperm also can be developed from mouse embryonic stem cells. However, scientists have been unable so far to produce live mice offspring from these gametes, and these experiments have not been repeated with human embryonic stem cells. The President's Council on Bioethics recommends in its "*Interim Recommendations (Revised)*," released on 15 January 2004, that Congress prohibit attempts to conceive a child by using gametes derived from embryonic stem cells. However, this recommendation, if implemented by Congress, would not affect the creation of embryos from gametes derived from embryonic stem cells for stem cell or other research.

EMERGING ETHICAL AND POLICY ISSUES RELATED TO STEM CELL RESEARCH

The Moral Status of Early Embryos

Clearly, ethical questions revolving around what is owed to early embryos have continued to undergird debate about embryonic stem cell research inside the Beltway since the presidential announcement. Advocates of specific positions regarding the moral status of embryos have first enunciated their stance and then moved to a conclusion about whether it would be right or wrong to disaggregate (destroy) embryos in stem cell research. This approach has resulted in repeated clashes of views from which no common ground on the issue has emerged.

A different way of reasoning about the question has been introduced both directly and indirectly by some discussants inside the Beltway. Instead of beginning with a specific stance about the moral status of early human embryos, they

ask what our stated policies for embryonic stem cell research and *in vitro* fertilization reveal about our underlying social presumptions regarding what is owed to early embryos. Our social presumptions, which reflect the interplay of community values, are integral to the way that we function as a society, and we therefore are reluctant to revise them unless we have convincing ethical and social reasons to do so. The discussants then consider whether existing explicit policies, such as those regarding federally funded embryonic stem cell research and the use of IVF, are in conflict with significant societal presumptions and thus need to be revised to better accord with them.

This approach has been reflected, for instance, in exchanges at congressional committee hearings regarding federal embryonic stem cell research policy. When legislators questioned NIH and administration figures about the sufficiency of approved embryonic stem cell lines, the latter frequently responded that since the President had not imposed barriers on privately funded embryonic stem cell research, any deficiencies in the number of these lines could be remedied in the private sector. This response seemed curious to some committee members, for, if it is ethically acceptable to destroy embryos in stem cell research conducted in the private sector, as these government representatives had indicated, the governing societal presumption is that it is not wrong *per se* to destroy embryos in stem cell research. Yet the presidential policy that it is ethically unacceptable to conduct research with federal funds on stem cells derived from embryos after a certain date conflicts with this presumption. These legislators therefore maintained that there is no reason to set aside the social presumption that it is ethically acceptable to destroy embryos in stem cell research when research is conducted in the public sector and that the federal embryonic stem cell research policy needs to be revised to be consistent.

A similar line of reasoning was introduced implicitly during a discussion of the theory of complicity by the President's Council on Bioethics. In a discussion on 4 September 2003, Michael Sandel observed that the embryonic stem cell lines available for use by researchers seeking federal funding had been approved as meeting the ethical guidelines set out in the "Fact Sheet" distributed at the time of President Bush's August 2001 speech. Yet if the view behind current federal stem cell research policy is that it is wrong to destroy embryos remaining at IVF clinics for research because these embryos are living human beings, it seems odd to have set up ethical guidelines for doing so. This seems akin, Sandel argued, to setting up ethical guidelines for killing individuals in prison camps to obtain their organs for transplantation. He questioned whether following such guidelines could undo the wrong of killing the prisoners for their organs and, on the view that embryos are human beings, asked the same about the embryos that figure in stem cell research. The fact that we have such guidelines, Sandel implied, suggests that, contrary to the stated justification for current federal embryo research policy, we do not presume that embryo destruction in stem cell

research is equivalent to murder. We therefore need to reconsider the existing stem cell research policy in light of our actual social presumptions about the destruction of early embryos, he suggested.

Social presumptions about the moral status of early embryos also have been elicited by some with regard to socially accepted practices and policies concerning IVF and then applied to stem cell research policy. For example, task forces from the Episcopal and Methodist churches recently issued brief reports circulated on the Hill pointing out that society in general has accepted for many years that IVF involves the discard of the early embryos that remain when treatments have been completed. We have presumed as a society, as have Episcopalians and Methodists as religious communities, that this practice is ethically acceptable, as evidenced by the fact that we have not attempted to stop it in the United States. The Episcopal report[6] maintains that, to be consistent, the same presumption should apply to the practice of stem cell research, making it ethically acceptable to bring about the demise of these early embryos not only by discard, but also by disaggregation for research. Authors of the Methodist report were more reluctant to accept what they view as the unbridled use of IVF by infertile couples with its accompanying creation of spare embryos. Their report consequently urges infertile couples to forgo this means of pursuing parenthood, but it acknowledges that some couples in good conscience will not. Therefore, the report concludes that, given the need to create more embryos than might be used in IVF procedures (in order to have extra embryos available for future IVF attempts and obviate the need for women to undergo future risky egg extraction procedures), it is "morally tolerable" to use those embryos remaining after IVF treatment has been completed in stem cell research, rather than simply to discard them. Both task forces moved, in related ways, from the presumption that it is acceptable to discard embryos remaining at the completion of IVF procedures to the conclusion that it is also acceptable to disaggregate embryos remaining at the completion of IVF procedures for use in stem cell research.

Proponents of reasoning from presumptions that are integral to the way that we function as a society suggest that it provides a way to develop embryonic stem cell research policy without engaging in a war between those with conflicting and irreconcilable stances on moral status. Although this way of reasoning has not reached the same level of sophistication or recognition inside the Beltway as have arguments that begin from explicit positions about the moral status of early embryos, the social presumptions approach is beginning to attract notice.

The Creation of Chimeras

Some investigators are contemplating engaging in what have been termed "chimera" assays in which adult human stem cells are transferred into animal blastocysts and followed to see whether and, if so, how they fuse with the cells of these hosts. The researchers maintain that certain kinds of adult stem cells that de-

velop primarily during the prenatal period, such as retinal and neural stem cells, cannot be studied adequately *in vitro* and need to be investigated in the dynamic environment provided by a prenatal living organism. These investigators hold that it would be unethical to transfer the cells to human embryos and they are therefore considering the use of animal embryos, such as those of the mouse and monkey. They maintain that this would not lead to the development of human-animal hybrids if the number of human cells and their state of differentiation were controlled, but instead would result in animals with some human cells. Other chimera experiments that have been proposed or carried out in the reproductive, rather than the stem cell, sphere, however, involve mixing human and animal embryos or gametes and would therefore result in human-animal hybrids.

The idea of creating such chimeras has aroused controversy, for it raises the question of where boundaries between humans and animals lie and, indeed, whether this question is ethically significant. Several commentators, including some members of the President's Council on Bioethics, have argued that such chimeras are unnatural and that their creation denigrates human dignity. Others point out that we have accepted the use of drugs and vaccines produced with animal materials, xenotransplantation in which animal organs are transferred to humans, and the movement of genes between humans and animals. Therefore, they argue, we need to make explicit where the ethical limits to such endeavors lie. The President's Council, in its "*Interim Recommendations (Revised)*" of January 2004, recommends that Congress temporarily "[p]rohibit the transfer, for any purpose, of any human embryo into the body of any member of a non-human species; and prohibit the production of a hybrid human-animal embryo by fertilization of human egg by animal sperm or of animal egg by human sperm." This recommendation, if enacted by Congress, would not prohibit the transfer of human stem cells into animal embryos but would ban the use of reproductive measures to create human-animal chimeras.

A variety of ways to address the creation of human-animal chimeras has begun to emerge in exchanges inside the Beltway and elsewhere. These discussions involve explorations of whether there are certain natural ends toward which humans and animals aim, whether repugnance based on intuition is sufficient to justify banning such chimeras, how and why we draw lines between species and which lines should not be crossed, and what we mean by human dignity. This is a newly developing area and no trend is yet discernible among those examining the ethical nuances of the creation of chimeras in stem cell research. It will take on even greater importance as stem cell research expands.

Fairness in Embryonic Stem Cell Banking

NIH is creating a Human Embryonic Stem Cell Registry that is accessible to investigators seeking federal funding and that lists those cells that meet the eligi-

bility criteria set out in the President's speech. NIH is not developing a stem cell bank, in that it only lists but does not distribute the approved lines.

Stem cell investigators have indicated that it would be useful to have access to a bank of well-characterized federally and privately funded embryonic stem cell lines that would obtain, test, and distribute these lines in a way akin to that of the Stem Cell Bank of the United Kingdom (Brivanlou 2003). It is unlikely that NIH would develop such a bank, for doing so would require the agency to authorize the use of embryonic stem cell lines that do not fall under the President's policy. It is unclear whether private funds could be found to establish such a bank listing and distributing embryonic stem cells available in the private sector in the near future.

In preparation for the more distant future, however, the working group at Johns Hopkins University has proposed establishing a stem cell bank in the United States for when stem cell research reaches the clinical stages (Faden 2003.) To achieve cell-based therapies rapidly and fairly, this bank would be composed of the fewest number of cell lines that would reflect the ancestral backgrounds of all of the major ethnic groups in the United States. Since a bank that ignored the ancestral backgrounds of donors would favor Caucasians due to the country's demographics, the group maintained that lines from those of other ancestral groups should specifically be included to address diseases that occur more frequently in non-white groups. This would allow fair access to stem cells by members of minority groups. Administrators of the bank would identify a range of gamete donors with diverse ancestral backgrounds, create embryos *in vitro* using their gametes, and then disaggregate the embryos to obtain stem cells for therapeutic use. It is arguable that this program would not violate the Dickey-Wicker Amendment, since it would not involve the creation of embryos for research but for therapy and that, therefore, as the law currently stands, such a bank could be developed with federal funds.

Some critics have responded that such a stem cell bank could reach many more patients if it were to disregard the ethnic background of gamete donors and simply collect as many stem cell lines as possible. Others have questioned whether there is any scientific basis for the ethnic classifications necessary to underlie this proposed stem cell line bank. Still others have expressed a concern that this bank would amount to an "embryo farm" that would wrongfully create embryos only to destroy them.

Regulatory and Patent Issues

The internal panel established at NIH to implement the President's embryonic stem cell policy is composed of scientists but includes no ethicists, patient representatives, or community representatives among its members. Its findings about whether the approved embryonic stem cell lines meet the ethical guidelines set out in the President's "Fact Sheet" of August 2001 are not readily accessible to

the public. Further, the President's Council on Bioethics did not include embryonic stem cell research in the sweep of its interim revised recommendations for the regulation of biomedical innovations issued in January 2004. The chair stated that the field is too young to provide a sense of where and why such oversight and regulation of stem cell research might be needed.

In its interim revised recommendations, the President's Council does recommend that Congress temporarily "[p]rohibit the use, or the preservation *of those embryos that are being used solely for the purposes of research,* beyond a designated stage in embryonic development . . .". In an accompanying note, the Council indicates that it was divided about whether the upper limits for embryo experimentation should be 10 or 14 days after the first cell division. If enacted, however, it would have no impact on any embryonic stem cell research in the private sector, for that research is carried out using stem cells derived from embryos at an earlier stage of development than 10 to 14 days after the first cell division.

Although the President's Council on Bioethics (2004) issued no new guidelines regarding stem cell research in its recent report, in an earlier draft of its recommendations about assisted reproduction, it recommended that the disposition of human embryos created in fertility laboratories be tracked. This provision, which would have had an impact on embryonic stem cell research, was dropped, however, in the interim revised recommendations of January 2004 in response to concerns raised about privacy by patient advocacy groups. Some maintained that this would have amounted to an attempt to create new protections for early embryos. This belief was reinforced by wording in the original draft document that referred to the human embryo as a "child to be" and a "future child." It remains to be seen whether the President's Council will develop new recommendations regarding embryonic stem cell research in the future, should it be asked to continue its work, or whether it will continue to refrain from recommending revision of the current federal policy.

The debate over the President's policy regulating public funding of embryonic stem cell research, some commentators maintain, has led Congress and the media to ignore embryonic stem cell research practices in the private sector. Yet, they argue, the policy has, in effect, relegated embryonic stem cell research in the United States to the private sector, where the bulk of such research is being funded. This has certain adverse ethical and public policy consequences.

One is that no common ethical safeguards for conducting embryonic stem cell research have been developed in the private sector. Although privately funded research is being carried out on stem cells derived from embryos by a broader range of techniques than those allowed in the public sector, these stem cells are not being obtained according to some generally accepted ethical rubric. Some individual companies are following guidelines for the use of embryos remaining at IVF clinics that originally were set up by an NIH-appointed panel during the

Clinton administration. These were not put into effect fully by the Bush administration. However, these guidelines do not apply to the derivation of stem cells from embryos that are obtained in other ways than through *in vitro* fertilization. The International Society for Stem Cell Research, formed by both privately and publicly funded stem cell investigators and related groups, has not yet attempted to develop ethical guidelines for stem cell research in the private sector to which its members would be asked to adhere. Thus, embryonic stem cell investigators supported by private funders often "wing it" ethically, leading some to declare that a national committee should be established to oversee all stem cell research in the United States so that the public is assured that this research is being carried out according to some ethical standards.

An additional concern has been expressed in Congress about the impact on patent rights in stem cell research of the President's policy and the consequent reliance of investigators on private sector funding. The investigators who first isolated human embryonic stem cells had to turn to a private company for research funding. In exchange for providing these monies, the company received significant rights with respect to the patent held on embryonic stem cells by the university where these investigators worked. Major control of embryonic stem cells by a few such private companies raises significant public policy questions, such as whether innovation might be stifled. Moreover, the lack of significant public funding of embryonic stem cell research has meant that these stem cell lines might not produce all the health benefits they otherwise might have exhibited. Companies that need to satisfy shareholders with short-term profitable results might not pursue such research in a way that would produce maximal long-term benefit. Furthermore, it has meant that those with serious degenerative conditions who do not have much market power are not likely to see stem cell research directed toward their needs. Thus, some commentators have observed that greater attention needs to be given to the ethical and public policy questions that are raised by private endeavors to carry out stem cell research.

CONCLUSION

New ethical questions are being raised about embryonic stem cell research, even as the old ones persist. The question of whether early embryos are owed the same protections that we accord to fully-developed living human beings still overshadows other questions in discussions of stem cell research inside and outside the Beltway. There is a hint that new ways of thinking about this question are developing, but it is difficult to state at this point whether these will provide a way to resolve the deadlock that has developed on the Hill about the ethics of pursuing embryonic stem cell research.

Federally funded researchers have maintained that both the narrowing of the number of embryonic cell lines available for federally funded stem cell research under President Bush's policy and the contamination of approved stem cell lines

with animal feeder cells have stifled stem cell research in the public sector and forced investigators to turn to the private sector for support. Yet no commonly accepted ethical guidelines for the broader range of embryonic stem cell research carried out in the private sector have emerged. This leaves the Congress and the public uncertain about whether this research is being conducted in a way that is consonant with public values and social presumptions. Ethical questions about the use of parthenogenesis, gametes derived from stem cells, and chimeras in private sector research are being raised, but no established ethics body in the private sector has yet addressed these practices in depth. Several ethicists, consequently, have urged private funding agencies and associations of stem cell researchers to establish an ethics oversight body for stem cell research in the private sector to develop ethics guidelines for such research.

Further, no interdisciplinary body is charged with reviewing federally funded stem cell research grant proposals in ways that are transparent to the public to ensure that they meet current and possible future ethical requirements for conducting this research. Should questions arise about whether adequate and appropriate consent has been derived from embryo donors for this publicly funded research, for instance, it is unclear where those making such enquiries could find documented answers. Several commentators and working groups have called on Congress and the administration to establish a public body for ethics oversight of stem cell research akin to the Recombinant DNA Advisory Committee, which is responsible for overseeing gene transfer research in the public sector and, on a voluntary basis, in the private sector. In today's politically charged climate, however, they express concern about whether a public body that represents the broad spectrum of mainstream views on embryonic stem cell research could be put into place, and whether, if appointed, it could function effectively.

There is near-universal agreement inside and outside the Beltway that stem cell research is an important and complex endeavor that offers the promise of treating, and perhaps curing, many patients who suffer from serious degenerative disorders. And there is near-universal agreement that the lure of beneficence that creates such excitement about stem cell research must be tempered by other important ethical considerations, such as respect for the dignity of human beings, patient choice, patient privacy, and the demands of justice. Beyond that, there seems to be little agreement inside or outside the Beltway about stem cell research—except about the conviction that the policy debates about this research need to be conducted in a full, fair, and open manner in a publicly transparent way in hopes of finding new ways to bridge significant differences and enabling stem cell research to fulfill its promise.

I thank Mary Anderlik Majumder and Peter J. Cohen for extremely helpful comments on an earlier draft of this article and LeRoy Walters and Françoise Baylis for useful discussions of the subject.

NOTES

1. It is often stated that President Bush issued an "executive order" setting out his stem cell research policy. However, his public pronouncements on embryonic stem cell research take the form of (1) the text of his speech on 9 August 2001 and (2) a "Fact Sheet" issued on the same day. No document labeled "Executive Order" (with a number assigned) appears on the White House website (*http://www.whitehouse.gov*) that lists all presidential executive orders.
2. Of these 12, four are held by universities in California and Wisconsin; five by the Singapore-based biotech firm, ES Cell Ltd.; two by an Australian biotech company, BresaGen Ltd.; and one by a South Korean hospital. A continuously updated list of available and eligible stem cell lines is provided at *stemcells.nih.gov*.
3. These three lines also were grown with mouse feeder cells.
4. As this article went to press, the *Washington Post* (Gillis and Weiss 2004) reported that an unpublished NIH analysis circulating on Capitol Hill reveals that only 23 of the 78 embryonic stem cell lines approved by President Bush for federally funded research would ever be available to U.S. researchers. Sixteen of the 78 lines have died or failed to reproduce, making them useless to scientists. Moreover, of the 15 lines currently available, several are beginning to show genetic abnormalities that might make them unsuitable for both research and clinical use.
5. As of the end of December 2003, Louisiana, Michigan, and South Dakota had passed legislation prohibiting research on embryos. Arkansas, Iowa, and North Dakota had passed laws prohibiting the use of cloned embryos for research. California and New Jersey had passed laws allowing embryonic stem cell research, and Maryland, Massachusetts, New Jersey, New York, Pennsylvania, Rhode Island, Tennessee, Texas, Vermont, and Washington had introduced legislation allowing stem cell research.
6. I was involved in writing this report.

REFERENCES

Alvarez-Dolado, M.; Pardal, R.; Garcia-Verdugo, J. M.; et al. 2003. Fusion of Bone-Marrow-Derived Cells with Purkinje Neurons, Cardiomyoctes and Hepatocytes. *Nature* 425: 968–73.

Battey, James F., Jr. 2004. Letter to Suzanne Kadereit, Ph.D., Editor, International Society for Stem Cell Research, Boston, MA, 15 January. Available at *http://www.isscr.org/newsletters/battey_letter.doc*. Accessed 3 February 2004.

Brivanlou, Ali H.; Gage, Fred H.; Jaenisch, Rudolf; et al. 2003. Setting Standards for Human Embryonic Stem Cells. *Science* 300: 913–16.

Cowan, Chad A.; Klimanskaya, Irina; McMahon, Jill; et al. 2004. Derivation of Embryonic Stem-Cell Lines from Human Blastocysts. *New England Journal of Medicine* (25 March). Available at *www.nejm.org* to subscribers. Accessed 7 March 2004.

Dawson, Liza; Bateman-House, Alison S.; Agnew, Dawn Mueller; et al. 2003. Safety Issues in Cell-Based Intervention Trials. *Fertility and Sterility* 80: 1077–85.

Faden, Ruth R.; Dawson, Liza; Bateman-House, Alison S.; et al. 2003. Public Stem Cell Banks: Considerations of Justice in Stem Cell Research and Therapy. *Hastings Center Report* 33 (6): 2–15.

Gillis, Justin, and Weiss, Rick. 2004. NIH: Few Stem Cell Colonies Likely Available for Research. *Washington Post* (3 March): A3, A13.

Hoffman, David I.; Zellman, Gail L.; Fair, Christine A.; et al. 2003. Cryopreserved Embryos in the United States and their Availability for Research. *Fertility and Sterility* 79: 1063–69.

Hwang, Woo Suk; Ryu, Young June; Park, Jong Hyuk; et al. 2004. Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst. *Science* (12 February). Available at *http://www.scienceexpress.org* to subscribers. Accessed 12 February 2004.

President's Council on Bioethics. 2004. *Monitoring Stem Cell Research: A Report of the President's Council on Bioethics* (Pre-Publication Version). Washington, DC. Available at *www.bioethics.gov*. Accessed 17 January 2004.

White House. 2001. Remarks by the President on Stem Cell Research (9 August). Available at *http://www.whitehouse.gov/infocus/healthcare/archive.html/-61.3KB*. Accessed 29 December 2003.