The complex moral and ethical debate surrounding the definition of the origins of human life, together with conflicting current and proposed legislation on state and federal levels, is hindering the course of research into the therapeutic uses of human embryonic stem cells. However, newly identified sources of adult stem cells, free from many of the ethical and legal concerns attached to embryonic stem cell research, may offer great promise for the advancement of medicine. These alternative sources may alleviate the need to resolve the stem cell debate before further therapeutic benefits of stem cell research can be realized. While legislation and ethics evolve to address the legal and moral issues of embryonic stem cell research, innovative researchers will continue to search for and find real and present solutions for cell-based therapies using adult stem cells.

Embryonic stem cell research has long been the subject of an intense debate that raises complex moral, legal, ethical, and political questions. Embryonic stem cells have been hailed as a promising source of therapy for a wide variety of human diseases, including Parkinson's, diabetes, and Alzheimer's. However, because the harvesting of embryonic stem cells involves the destruction of the embryo from which the cells are collected, this area of research confronts similar questions to those posed in the abortion debate: What is a human life? When does life begin? There are those who believe that harvesting embryonic stem cells destroys human life, whereas others believe that the research is for the greater good because only embryos destined to be destroyed would be used. Still others argue that any embryonic research will ultimately lead to the creation of embryos solely for the purpose of research.

Regardless of one's position on these issues, the fact remains that difficult ethical and legal questions hinder the advancement of stem cell science, frustrating both scientists and patients who are anxiously awaiting cell-based therapy solutions. Some legal and ethical questions pertaining to embryonic stem cell research may never be answered: What, if any, limitations should be placed on this type of research? Is it appropriate for government to fund research that is the subject of such controversy? How can fair access to stem cell therapies be ensured?
The Science of Stem Cells

Medical research has increasingly attempted to address injury and disease with treatments beyond pharmacologic or other traditional methods. One area of promise is cell-based therapy, particularly, the application of stem cell biology. Through stem cell research, scientists hope to discover methods to repair and regenerate diseased or damaged tissue and organs, and to prevent disease from occurring.

A stem cell has 3 specific characteristics: self-renewal, an undifferentiated state, and potential to differentiate into a specialized cell. The diploid cell, or zygote, created from the fusion of the male and female gametes, has the innate ability to form any cell type. After several rounds of cell division, the zygote-derived cells differentiate into trophoblasts, becoming the placenta and the inner cell mass (ICM), which forms the embryo. The cells of the ICM are pluripotent, and thus have the ability to differentiate into cells of every lineage of the body except extra-embryonic tissue. Derivative cells of the ICM are referred to as human embryonic stem (hES) cells, which are also pluripotent. Even though tissue-specific stem cells, also known as adult stem cells, are generated from hES cells, these tissue-specific stem cells are believed to be multipotent—able to differentiate into one subset of tissue lineages. Although adult stem cells are invaluable in organism development, pluripotent cell characteristics are more attractive to researchers because they lack the limitations understood to be inherent in multipotent cells.

Limitations of Current Federal Legislation

President George W. Bush announced the current federal policy on hES cell research on August 9, 2001. In his address, President Bush limited research funding to existing stem cell lines that had been derived from excess embryos created for in vitro fertilization. The Bush policy prohibits funding for human cloning, the derivation of stem cell lines from human embryos, and the use of any stem cell lines derived after the date of his address. The stated purpose of the President’s policy is to preserve the “value and sanctity of human life” while promoting “vital medical research.”

The President’s announcement has not been without controversy. Although the Bush administration was the first to fund hES cell research, federal funding was legally permissible under previous federal law for all hES cell research other than the derivation of stem cells from human embryos. By limiting federal funding to those stem cell lines created before August 9, 2001, the President’s policy is much more restrictive than required by federal legislation.

Recently Proposed Federal Legislation

On June 29, 2006, the US Senate reached a unanimous consent agreement to consider 3 bioethics bills for debate and vote: S 3504, S 2754, and HR 810. S 3504, also known as the Fetus Farming Prohibition Act of 2006, passed unanimously in both the Senate and the US House of Representatives on July 18 and was signed into law on July 19. The act will prohibit “fetal farming,” the creation of embryos or fetuses specifically for use as a source of cells or tissue. S 2754, the Alternative Pluripotent Stem Cell Therapies Enhancement Act, was also passed unanimously by the Senate on July 18, but was blocked in the House of Representatives. This bill would have required the National Institutes of Health (NIH) to research and fund alternative stem cell lines from human embryos.

In 1999, General Counsel Harriet Rabb of the US Department of Health & Human Services determined that the so-called “Dickey Amendment” to the Departments of Labor, Health & Human Services, and Education, and Related Agencies Appropriations Act did not prevent the National Institutes of Health from funding embryonic stem cell research. The Dickey Amendment prohibits the use of federal funds for “research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death.” Rabb concluded that stem cells themselves do not meet the statutory, medical, or biological definition of a human embryo. Consequently, although federal funds could not be used to derive stem cells from a human embryo (thus destroying it), federal funding could support research on existing stem cells.
methods of producing pluripotent stem cells without destruction of human embryos. After its defeat, the House Rules Committee approved a rule that will allow the bill to be reconsidered at a later date.

HR 810, also known as the Stem Cell Research Enhancement Act of 2005, was the most controversial of the proposed bills and would have altered current federal policy by permitting federal funding for hES cell research regardless of when the stem cell lines were derived, provided that the embryos used were: (1) originally created for in vitro fertilization; (2) would otherwise be discarded; and (3) were donated by fully informed, consenting individuals who received no financial or other inducements. Although HR 810 was approved by both the House of Representatives and the Senate, President Bush, who is strongly opposed to the use of taxpayer dollars to pay for research that destroys human embryos, vetoed the bill on July 19. An attempt by the House of Representatives to override the Presidential veto failed, 51 votes short of the required two-thirds majority.

**State Legislation Focusing on Cell Research**

Currently, there are no federal laws or regulations governing privately or state-funded hES cell research. In light of the President’s recent veto of the Stem Cell Research Enhancement Act, state laws have become the focus of the regulation of hES cell research. State laws governing hES cell research vary widely and span a broad continuum ranging from criminalization to encouragement and significant funding. Some of the highlights of state law are discussed in the following paragraphs.*

One state that has taken a strong position with regard to hES cell research is South Dakota, which enacted legislation in 2000 criminalizing any nontherapeutic research: (1) in which human embryos are destroyed or subjected to substantial risk of harm; or (2) uses cells or tissues obtained from the destruction of or harm to a human embryo. Although South Dakota is the only state that has entirely banned hES cell research, 25 other states have laws imposing some form of restriction.

On the other end of the spectrum, 5 states—California, Connecticut, Illinois, Maryland, and New Jersey—have policies in place to encourage and financially support hES cell research. For example, California’s Health and Safety Code expressly permits “the derivation and use of hES cells, human embryonic germ cells, and human adult stem cells from any source.” In addition, in November 2004, California voters approved Proposition 71, also known as the California Stem Cell Research and Cures Act. This state constitutional amendment permits the sale of $3 billion in general obligation bonds to provide funding for stem cell research facilities in California. Until recently, this funding has been stalled because of lawsuits filed on state constitutional grounds by 2 taxpayer groups and the California Family Bioethics Council. The consolidated suits are currently pending before the California First District Court of Appeals. On July 20, 2006, in response to the President’s veto of federal stem cell legislation, Governor Arnold Schwarzenegger authorized a $150 million loan to the California Institute of Regenerative Medicine, the agency charged with implementing the state program.

In July 2005, Governor Rod Blagojevich issued an executive order authorizing the creation of the Illinois Regenerative Medicine Institute to award grants to stem cell research facilities. The order permits funding for research involving “adult stem cells, cord blood stem cells, pluripotent stem cells, progenitor cells, the product of somatic cell nuclear transfer or any combination of those cells.” Ten grants...

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*Note that South Dakota law bans only “nontherapeutic research,” defined as “research that is not intended to help preserve the life and health of the particular embryo subjected to risk.” “Nontherapeutic research” also does not include in vitro fertilization or diagnostic testing.
totaling $10 million were awarded pursuant to the executive order in April 2006. More recently, in response to the President’s veto, Governor Blagojevich announced on July 20, 2006, that an additional $5 million will be made available for fiscal year 2007.  

In other states, citizens and lawmakers continue to debate the position their jurisdictions will take on embryonic stem cell research. One such state is Missouri, where in November 2006, voters will consider the Missouri Stem Cell Research and Cures Initiative, a constitutional amendment expressly permitting Missouri researchers to conduct any stem cell research that is also permitted under federal law. If passed, the referendum will also guarantee that Missouri patients will have access to any stem cell therapies and cures permitted by federal law. On August 8, 2006, the Missouri Secretary of State confirmed that supporters of the measure had gathered enough signatures to ensure its appearance on the November ballot.

**Potential Drawbacks of Federal and State Policies**

Some experts fear that the United States’ “patchwork quilt approach” to stem cell legislation, with little federal support or oversight and wide variation in state policies, may have an untoward effect on the progress of medical research. One of the greatest concerns among scientists is the dwindling number of federally approved stem cell lines available for research. In 2001, the Bush Administration estimated that more than 60 stem cell lines would be eligible for funding. However, only 20 eligible lines are currently available for use, and of those, only half a dozen are routinely used by researchers. Moreover, stem cell lines develop mutations the longer they are grown in the lab, and these mutations may render the existing stem cell lines useless within a short span of years. In addition, even otherwise viable stem cells may have limited clinical use because of potential contamination: the federally approved lines, originally grown on mouse feeder cells, may harbor mouse viruses that the human immune system would be unable to fight. Nonetheless, some researchers believe that the available stem cell lines are adequate for the conduct of basic research, and despite the limited number of lines available, the NIH funding for hES cell research has grown 60% since 2004.*

Still, many are of the opinion that federal policy is placing the United States at a competitive disadvantage. Scientists in countries whose stem cell policies are more liberal than those in the United States have made significant advances in stem cell research and have published far more in the field than their American counterparts. Another potential drawback of restrictive state and federal policies is “brain drain,” the exodus of the best American scientists first to other states, and then to other nations where stem cell regulation is less stringent. Commentators also fear that lack of funding and unpredictable policy will discourage American scientists from entering the field of stem cell research altogether.

Financial and biological access to stem cell therapies is also problematic. Financial access to therapies may be affected by private companies that will finance stem cell research for which federal funding is prohibited. Because the private sector tends to invest primarily in therapies that will be profitable, other therapies that may have important therapeutic value but do not promise much commercial success may remain undeveloped.

Biological access is threatened by the potential rejection of stem cell therapies by a patient’s immune system. Though little information is available concerning the genetic makeup of the stem cell lines eligible for federal funding, researchers expect that these stem cell lines are unlikely to match a large number or cross-section of patients. In addition, the majority of the embryos from which these stem cell lines were derived were harvested at fertility clinics in the United States, Sweden, and Israel (countries where clinical populations are predominantly

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*Embryonic stem cell research received funding of $20 million, $24 million, and $40 million in 2003, 2004, and 2005, respectively.
white) and in Singapore and India (countries where clinical populations are largely East and South Asian), and thus, are not racially diverse.45 The small number of available stem cell lines is also worrisome.36

**Innovative Research: Possible Solutions to the hES Cell Debate?**

Ethical concerns and funding limitations for research using hES cells have prompted investigators to seek other sources of stem cells.* Recent research findings indicate promise for adult stem cells from sources such as the placenta,46,47 hair follicles,48 adipose tissue,49 brain cells,50 and skin.51 Other studies focusing specifically on pluripotent sources raise the possibility of reprogramming adult stem cells to pluripotency52 and expand on existing stem cell research in bone marrow by demonstrating the potentially pluripotent nature of these stem cells.53–55 Innovative adult stem cell research has also found that the human umbilical cord (UC) holds great promise as an alternative source of stem cells. UC research is discussed in this article as a means of highlighting how these novel sources of stem cells may provide a present solution to the hES cell debate.

One group of researchers, Kogler et al,56 has examined human cord blood and identified an intrinsically pluripotent cell population, referred to as unrestricted somatic stem cells (USSCs). Although rare in the cord blood population, USSCs can rapidly be expanded to 10¹⁵ cells without losing pluripotency. After ex vivo expansion, differentiation into bone, cartilage, hematopoietic cells, and neural, liver, and heart tissue was demonstrated in animal models.

Another group of investigators, a Canadian team from Toronto, has also made progress in identifying new sources for cell-based therapies.57 These researchers examined cells from Wharton’s jelly, the primitive connective tissue of the human UC. Using a new harvesting technique in this previously unexplored tissue, this group was able to isolate human UC perivascular (HUCPV) cells, a subpopulation of cells exhibiting a functional mesenchymal phenotype. In previous studies, the UC was discarded or not specifically targeted because researchers focused solely on cord blood.57,58 However, the Canadian team recognized that these readily accessible HUCPV cells from Wharton’s jelly were an abundant source of mesenchymal progenitor cells,57 which have the potential to develop into adipocytes, chondrocytes, osteoblasts, and myocytes.59 Thus, HUCPV cells provide a novel source of cells that may be effective in treating a wide range of musculoskeletal and other diseases.

It is worth noting 2 additional benefits that these HUCPV cells offer. First, HUCPV cells provide a population of human immunoincompetent or “nonimmunogenic” progenitor cells that are devoid of the antigen markers that cause immune rejections,60 thereby removing the limitation of recruiting viable donors.57,61 Second, HUCPV cells are more prolific than cord blood cells. Unlike cord blood, mesenchymal stem cells can be harvested from every UC.57 Furthermore, the frequency of mesenchymal stem cells is 1 in 300 when harvested from HUCPV cells, compared with 1 in 200 million when derived from cord blood.

These novel sources of stem cells are promising, not only for their scientific and therapeutic value, but also because they avoid many of the legal and ethical issues that are hindering the progress of stem cell science. Because they are adult stem cells, USSCs and HUCPV cells are morally uncontroversial in that their derivation does not involve the destruction of human embryos. Therefore, federal and state funding should flow more freely for these innovative techniques than it has for hES research. Moreover, the fact that HUCPV cells are prolific in UC tissue and lack the genetic markers that cause immune rejection is especially significant, given that stem cell supplies derived from HUCPV cells will be not only abundant, but also available for unrelated patients—and thus financially and biologically accessible.

Additionally, existing legislation governing the collection of cord blood can be translated
effortlessly to research involving UC tissue. At the federal level, the Stem Cell Therapeutic and Research Act of 2005 authorizes $79 million in funding for the collection and storage of cord blood. The Act calls for the US Department of Health & Human Services to contract with qualified cord blood banks with the goal of collecting 150,000 units of high-quality blood to be made available for transplantation. The Act allows for cord blood that cannot be used clinically to be provided to stem cell researchers. Many states, including Florida, Illinois, Massachusetts, and Missouri have also enacted legislation governing the collection of cord blood. Most recently, in April 2006, Georgia Governor Sonny Perdue signed an executive order creating the Governor’s Commission for Newborn Umbilical Cord Blood Research and Medical Treatment. The Commission will establish a statewide network of banks for the collection and storage of postnatal tissue and fluid for clinical and research purposes.

CONCLUSIONS

Our nation is often strongly divided on issues that involve the definition of human life. Although adult stem cell research has been conducted for quite some time, the application of cell-based therapies and hES cell research is in its infancy. To date, adult stem cells have benefited patients with bone marrow transplants, leukemia, lymphoma, other blood disorders, diabetes, and advanced kidney cancer. More recently, new clinical applications are being tested for the treatment of liver disease, coronary disease, autoimmune and metabolic disease, lupus, and other advanced cancers. The latest research findings highlight the promise that is perhaps yet to be realized in the field of adult stem cell research. The UC research mentioned herein is such an example. These alternative sources for cell-based therapies fit within the current legislative framework and avoid the ethical issues associated with hES cell research. Perhaps of greater importance, USSCs and HUCPV cells may provide real and present solutions for the continued development of cell-based therapies as scientists, patients, and the public anxiously await legislation and ethical standards that will guide this area of research.

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