The Promise and Peril of Embryonic Stem Cell Research: A Call for Vigilant Oversight

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Embryonic stem cell research raises issues that are fundamentally different from those affecting other areas of medical research. For the first time in history, we are faced with research that may profoundly affect the course of human life and disease by allowing us to more deeply understand and manipulate the basic building blocks of life itself. Although this research may produce powerful cures, it also holds great potential for unintended and even adverse outcomes.

Similar moral and ethical issues have challenged other areas of research, but the dilemmas posed by embryonic stem cell research are among the most challenging. It is an issue that cannot be left only to scientists, or ethicists, or patients, or religious leaders, as it is one that compels us to balance moral, ethical, scientific, and religious considerations. It is, therefore, vitally important that we are aware of the depth of the scientific, ethical, and moral issues involved.

In recent years, Congress has demonstrated a strong, bipartisan commitment to furthering biomedical research. But the unanimity surrounding medical research funding has been challenged by the issue of embryonic stem cell research—an issue that firmly confronts the ethical construct of biomedical research with the concepts of life and death, health and healing. In this piece, I provide an overview of the political and scientific history of the embryonic stem cell issue, evaluate the current political landscape, and discuss the future of this research.

I. HISTORY AND SCIENCE

On November 6, 1998, a team of researchers led by Dr. James Thomson at the University of Wisconsin published a paper outlining the successful isolation of pluripotent stem cells from human embryos, thus

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thrusting embryonic stem cell research to the forefront of debate.[1] As is well known by now, embryonic stem cells are derived from the inner cell mass of a blastocyst-stage (five to six days old) embryo. Although these inner cells have lost the ability to form supporting tissues, they retain the ability to develop into any cell type found in the body and are considered pluripotent. Over time, and if allowed, they may multiply and differentiate further, becoming committed to specific lineages. These pluripotent embryonic stem cells, when properly isolated and cultured, appear to contribute to all cell types found in the adult and seem to be capable of indefinite self-renewal.[2]

It is also now known that there exist relatively undifferentiated and self-renewing cells known as adult stem cells throughout the adult body—cells that help repair tissues harmed by injury, disease, or natural cell death. The most widely known and understood example of such a cell is the hematopoietic stem cell, found in bone marrow and responsible for the production of blood cells. Other promising cell types include neural stem cells and mesenchymal stem cells. Reports have also appeared touting the potential of stem cells from fat tissue, as well as those from umbilical cord blood.[3]

Until recently, adult stem cells were considered rare and inflexible, believed only to be able to form the cell types for the tissue in which they were found. Moreover, most adult stem cells have not grown well in culture and have remained difficult to obtain in significant quantities. However, recent news reports suggest that adult stem cells may have more plastic properties than previously believed, and the techniques for growing adult stem cells are being improved. For example, on January 23, 2002, *New Scientist* reported that researchers had discovered mulitpotent adult progenitor cells in adult bone marrow. Such cells appear capable of differentiating into all cell types and may avoid some of the difficulties associated with embryonic stem cells. Moreover, adult stem cells from human marrow have been expanded extensively in laboratories. While adult stem cells may not be capable of indefinite self-renewal, they do not also exhibit the tendency of embryonic stem cells to become malignant.[4] Ultimately, there remain many challenges and uncertainties surrounding both adult and embryonic stem cells.

II. POTENTIAL APPLICATIONS OF EMBRYONIC AND ADULT STEM CELLS

Both human embryonic and adult stem cell research hold tremendous potential for a wide range of uses, including clinical applications of cell-based therapies for diabetes, Parkinson's disease, Alzheimer's disease, leukemia, spinal cord injuries, and a number of other diseases and injuries.

This research may be useful in providing scientists with a better understanding of the human cellular growth and differentiation process, thus allowing researchers to seek out and attempt to treat or prevent the causes of birth defects, genetic abnormalities, and diseases. The research may also be useful in pharmaceutical development, allowing researchers to grow large numbers of various cell types in order to test drug effectiveness and toxicity.[5]

It is critical, however, that advocates not embellish the potential of either embryonic or adult stem cell research for medical therapies. This evolving science is still very young (the original Thomson discovery was published only three years ago). Further basic research must be conducted before we can hope to see clinical trials and possible treatments. In fact, with the exception of hematopoietic stem cells that have been used for many years in bone marrow transplantation, no other stem cells, neither embryonic nor adult, have yet demonstrated therapeutic applications.

Some of the challenges remaining for both avenues of research include: (1) learning the signals governing the differentiation of stem cells; (2) overcoming the challenge of immune rejection in cell transplantation; and (3) establishing consistent, effective methods to culture, isolate, and grow the cells in a timely manner that is consistent with good manufacturing processes.[6] The bottom line is that treatments, if they will be discovered, are likely several years away. Yet, the hope that they will someday yield therapies for those suffering from disease is powerful.

III. THE IMPORTANCE OF FEDERALLY FUNDED RESEARCH

Our nation's unique combination of public and private funding for scientific research is the envy of the world. It attracts the best researchers and has led to an explosion of medical and scientific innovations that are producing new treatments and hope for patients suffering from a wide range of disease.[7] Policymakers and the public are increasingly aware of the great potential of biomedical research, and this awareness has spawned an insatiable appetite for more and faster advances.

Because of this, Congress has worked during the past several years to double federal funding for the National Institutes of Health (NIH). In fact, the fiscal year 2003 budget proposed by President Bush completes this process, increasing NIH funding from $13.6 billion in fiscal year 1998 to $27.3 billion in fiscal year 2003. But to this point, many researchers have been discouraged from entering this new field of embryonic stem cell research because of the lack of federal funding. This is precisely why federal funding is so critical. It is clear that federal involvement in embryonic stem cell research will expedite scientific advancement by

making the research available to scores of the nation's best and brightest investigators, and improve research by ensuring that adult stem cell and embryonic stem cell research are conducted along side each other.

Federal funding should also bring a much-needed level of ethical safeguards and federal oversight to the field. To date, embryonic stem cell research has taken place with no federal supervision or regulation. Reports of researchers deriving embryonic stem cell lines from human embryos created specifically for research have made this pressing need clear. The continually evolving interaction between this promising but uncharted new science with the ethical and moral considerations of life demands a strong, comprehensive, publicly accountable oversight structure. It demands a policy that is responsive on an ongoing basis to moral, ethical, and scientific considerations. It is, therefore, up to policymakers to ensure that this research is subject to the highest standards of public transparency and effective regulation.

IV. THE INTERPLAY OF SCIENCE, ETHICS, AND PUBLIC POLICY

As the desire for new therapies and treatments grows, we must recognize that science is not practiced in a vacuum. Moral and ethical considerations cannot be ignored. With the ever-increasing pace of progress have come new challenges of ethics and technologies that have, at times, threatened the ability of public policy to respond. But, I deeply believe that we, as legislators, have an obligation to do just that.

There are those who argue that "politics" should not impinge on scientific process. I disagree. It is the role of politics to ensure that taxpayer money is used in a manner that is responsive to public interest and is acceptable to society. It is the role of politics to ask the question posed by the *Washington Post* several years ago: "Is there a line that should not be crossed, even for scientific or other gain, and if so, where is it?"[8] In fact, politics should and does have an important role in deciding what research is not only scientifically promising but also socially acceptable.

As a transplant surgeon, I have confronted many life-and-death decisions. I have performed hundreds of organ and tissue transplants and experienced the ethical dilemmas involved in end-of-life care. Having practiced in the early days of heart and lung transplantation, I have witnessed the powerful impact of medical progress on each of my patients. Moreover, I have seen firsthand the impact that medical and technological progress have had on reshaping legal and ethical criteria, as well as how ethics has shaped the practice of medicine.

As a surgeon, I frequently removed a heart from a brain-dead

individual and placed that heart into another patient who would have otherwise died. That required a determination of when brain death occurred—a routine process today that was very controversial when it was first developed just three decades ago.

Historically, death was not particularly difficult to determine or define. Generally, all vital systems of the body—respiratory, neurological, and circulatory—would fail at the same time, and none of these functions could be prolonged without the maintenance of the others. However, technological advances in life support, particularly the development of ventilators, have made it possible to keep some bodily systems functioning long after others have ceased.

These technical advances opened up the possibility of organ transplants and also created a need for the development of a neurological standard for determining when death occurs. Only after death has been determined is it appropriate to consider organ donation. On this basis, there is now broad public support for organ donation. It must be remembered, however, that the cohesive interplay of science, ethics, and policy did not come easily.

A similar dilemma now confronts us in the field of embryonic stem cell research. The question is much like that faced in the early days of organ transplantation: Do we remove organs and tissue for transplantation and research from an individual who is brain dead, but whose other organs continue to live and function normally? The question today is whether to fund research using stem cells derived from blastocysts that could, if implanted, become a fetus, but that will otherwise be discarded. I believe the provision of funding for such research is the proper course, but only under the strictest of regulations to ensure a clear separation of the decisions to discard excess embryos, donate them for adoption, or donate them for research, in an approach consistent with the precedent of organ donation.

V. THE PRESIDENT'S DECISION

In the first half of 2001, the question of federal funding for embryonic stem cell research reached new heights of attention as pressure mounted for President Bush to determine whether to implement the NIH Guidelines on embryonic stem cell research, promulgated under the previous administration. With growing public interest, members of Congress were also forced to confront these issues. As the only physician in the U.S. Senate, I felt particularly compelled to study the issue and make my position clear. On July 18, I announced a comprehensive framework for the support of embryonic stem cell research.[9] This position, based on

the following ten points, would allow stem cell research to move forward in a manner respectful of both the moral significance of human embryos and the potential of stem cell research to improve health: (1) a ban on the creation of embryos for research purposes; (2) the continuation of the present ban on federal funding of the derivation of embryonic stem cells; (3) a ban on all human cloning; (4) an increase in adult stem cell research funding; (5) funding for embryonic stem cell research only from blastocysts that would otherwise be discarded; (6) a rigorous informed consent process; (7) a limited number of stem cell lines; (8) a strong public research oversight system; (9) ongoing, independent scientific and ethical review; and (10) strengthened and harmonized fetal tissue research restrictions.

On August 9, 2001, President Bush announced a decision that may dramatically alter the course of biomedical research. After a lengthy process of thorough study, consultation, and reflection, the President decided to permit the NIH to fund research using embryonic stem cell lines already in existence on that date.[10] His decision means that, for the first time, the nation's premier federally supported scientists will be able to perform research using embryonic stem cells. It means that, for the first time, this research will be conducted by a broad number of scientists—and not merely by those using private funds. Because the President's focus was on the use of existing cell lines, some of the protective criteria I detailed are not necessary—for example, as rigorous an informed consent process since the cell lines already exist. But the President's position expressly or implicitly endorses a number of my criteria, such as a ban on the creation of embryos for research, a ban on human cloning, and a ban on federal funding for the derivation of embryonic stem cells. These standards, in particular, and the President's decision ensure a strong and cohesive moral construct, in general, that will become even more critical as science and research in these areas progress.

As attention has focused on this research in the last year, a great deal has been learned about both adult and embryonic stem cells. During the President's deliberations, the NIH determined the existence of more than sixty embryonic stem cell lines worldwide—considerably more than previously thought.[11] There are presently more than seventy lines in the NIH registry. But this process has also reminded us how little is known about this science and has driven home the fact that there is still far to go.

In the wake of the President's decision, some have challenged the viability of all those cell lines. Others have argued that these cells lines are not enough to meet research needs.[12] Still others are disappointed that the President decided to allow the use of federal funds for research on any

embryonic stem cells.[13]

The President's decision means that embryonic stem cell research will expand dramatically. This research may open the door to therapies and cures beyond our imaginations. For the first time, federal funds will be used to better understand the earliest stages of human life, and the existence of a public embryonic stem cell registry should ensure that research and discoveries are shared broadly and rapidly.

We should commend the NIH for taking important steps to move this research forward through the establishment of a stem cell registry where researchers around the world, as well as the general public, can access information about embryonic stem cell lines available for research. This registry has already been important in bringing a new level of public transparency to the research and expanding our knowledge about the global state of the science. Because of the NIH's work in establishing the registry, we know the location of more than seventy embryonic stem cell lines that are currently available. Moreover, the registry includes information on how they were derived, what their basic characteristics are, and how to contact their owners.

The registry represents a commitment by the NIH and the President to facilitate scientists' access to embryonic stem cells. Moreover, the NIH has built upon the registry by negotiating a Memorandum of Understanding (MOU) with the Wisconsin Alumni Research Foundation, which holds patent rights to the cell lines developed by Thomson. The MOU enables the NIH and NIH-funded investigators to access these cell lines under minimal conditions.[14] Hopefully, this agreement will serve as a model for such arrangements in the future.

But this research carries great moral as well as great medical danger, namely the potential to inflict harm. Because we have barely begun to understand its capacities, pioneers in the field must approach this research with the awe and respect it deserves. We must move forward with caution and restraint, remembering that it is untried, untested, and unproven. We must proceed within the context of a fully transparent, carefully regulated framework that ensures respect for the potential of this research and for the moral significance of the human embryo.[15]

Much of the public discussion and analysis of the President's decision has centered on whether his stipulations are sufficient for the success of this research. Issues such as autoimmune rejection and cell line diversity have been raised as potential obstacles.[16] While the fact that existing cell lines have been cultured and grown on mouse feeder cells has concerned some, the Food and Drug Administration (FDA) has said that this is not a barrier to this research. In fact, there are presently several active

Investigations for New Drugs for xenotransplantation products presently in clinical trials.[17]

While the concerns about the potential restraints of research limited to existing cell lines may one day prove valid, they will not prohibit the research from moving forward. Research knowledge will expand exponentially as we move beyond the relatively few cell lines isolated at the University of Wisconsin and begin to use the more than seventy lines available worldwide.[18] Moreover, the NIH currently spends more than $250 million per year on stem cell research—a figure that will continue to rise in the coming years as overall NIH funding continues to expand.[19] Ultimately, far more research must be done before we know the answers to the concerns—but, it is now up to the researchers to move forward. Should there come a time that a real obstacle to the continuation and success of embryonic stem cell research emerges, Congress might look to alleviate such a situation in a manner consistent with the rigorous standards that I have outlined. But there is much work to be done before we will know whether this is necessary. This is, after all, a new and evolving science.

The President has also taken a crucial step towards the long-term success and viability of embryonic stem cell research by recognizing the need for continuing moral and ethical oversight of this and other pressing issues in the fields of bioethics and medical advancement. The new Council on Bioethics, to be led by Dr. Leon Kass of the University of Chicago, will play an integral role in monitoring and advising the nation about the moral and ethical considerations that may be raised by a wide range of scientific breakthroughs.

VI. THE FUTURE OF STEM CELL RESEARCH

One critical aspect of the embryonic stem cell framework that was perhaps overlooked, or afforded less attention, when I announced my position in July 2001, was cloning. It is imperative that federal legislation be enacted to ban all human cloning. There are three primary reasons I believe a ban is necessary. First, the technique by which cloning is done, somatic cell nuclear transfer, remains highly inefficient and risky to the embryo—with very high failure, death, and mutation rates. Second, allowing human cloning opens the door to the exploitation of women as egg donors by creating a market for already in-demand oocytes. This would lead to often poor minority women undergoing risky superovulation treatments because of the high financial incentives involved. Finally, there is broad agreement that the creation of embryos solely for research is unethical and should be prohibited.

In addition, science has progressed to the point that we know a human

cloning ban will not derail stem cell research. In 1998, when I authored one of the first pieces of federal legislation prohibiting cloning, concerns existed that a cloning prohibition would impede embryonic stem cell research. However, subsequent advances in our knowledge of the successful development of embryonic stem cell lines at the University of Wisconsin and the identification of more than seventy such existing cell lines to date have made clear that banning cloning will not materially curtail embryonic stem cell research. Science has advanced to the stage where we now know more definitively, not only that embryonic stem cell research will not be hindered, but also that such research can, and will, proceed aggressively without the use of human cloning.

We will have to wait several years to know whether embryonic stem cell research may yield practical therapies. In the meantime, we should move aggressively forward in implementing the President's policy and to examine its progress closely over the coming months and years. As the research moves forward, ongoing congressional and scientific oversight will be critical to reevaluating the progress and needs of this research. Just as important, ongoing discussion among scientists, policymakers, ethicists, religious leaders, and the American people will be critical to maintaining the proper balance between science and ethics and to ensuring the ultimate success of our biomedical research endeavors.

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