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The future of human embryonic stem cell research: addressing ethical conflict with responsible scientific research

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Summary

Embryonic stem (ES) cells have almost unlimited regenerative capacity and can potentially generate any body tissue. Hence they hold great promise for the cure of degenerative human diseases. But their derivation and the potential for misuse have raised a number of ethical issues. These ethical issues threaten to paralyze pubic funding for ES cell research, leaving experimentation in the hands of the private sector and precluding the public's ability to monitor practices, research alternatives, and effectively address the very ethical issues that are cause for concern in the first place. With new technology being inevitable, and the potential for abuse high, government must stay involved if the public is to play a role in shaping the direction of research. In this essay, I will define levels of ethical conflict that can be delineated by the anticipated advances in technology. From the urgent need to derive new ES cell lines with existing technology, to the most far-reaching goal of deriving genetically identical tissues from an adult patients cells, technology-specific ethical dilemmas can be defined and addressed. This staged approach provides a solid ethical framework for moving forward with ES cell research. Moreover, by anticipating the moral conflicts to come, one can predict the types of scientific advances that could overcome these conflicts, and appropriately direct federal funding toward these goals to offset potentially less responsible research directives that will inevitably go forward via private or foreign funding.

key words: **embryonic stem cells • nuclear reprogramming • bioethics • therapeutic cloning**

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EMBRYONIC STEM CELLS: A PLURIPOTENT EMBRYONIC TISSUE

Many misconceptions surrounding the issue of human ES cells should first be clarified. One common misconception is that ES cells are derived from aborted fetuses. The practice of abortion has no relationship, direct or indirect, to ES cells. All (without exception) ES cell lines are derived from 5-day embryos (blastocyts) that were voluntarily donated by couples undergoing *In Vitro* Fertilization (IVF) and would otherwise be discarded [1]. In IVF, several hundred eggs are fertilized in a petri dish. 5 days after fertilization (approximately the time at which an embryo fertilized in the womb would implant in the uterus), a few of these 'blastocyst' embryos are transferred into the mothers womb. If the transfer is successful (i.e. the embryo implants into the uterus) then the rest of the embryos are discarded. Many embryos are produced by IVF to ensure that one child may be born. Blastocysts consists of ~100 cells, which includes 30–34 cells of the inner cell mass (ICM), surrounded by a specialized tissue (trophectoderm) that protects the ICM and is what implants into the uterus. ES cells are made by separating the ICM from the blastocyst and adapting cells of the ICM to growth in a petri dish. Hence, ES cells are a tissue derived from a doomed pre-implantation embryo that was created *in vitro* for therapeutic purposes. Abortion is neither necessary nor implied by ES cell production or the research performed with ES cells.

A second misconception is that ES cells are 'totipotent', in other words, they have the potential to form an entire human being (for example; [2]). Because ES cells have been extracted away from the supporting trophectoderm, and on their own lack the ability to create trophectoderm, they no longer have this potential. For this reason, ES cells are termed 'pluripotent'; they can form all the tissues of the adult body, but they cannot form the trophectoderm, which is essential for embryonic development.

A third common misconception is that either the derivation or the intended use of ES cells involves the cloning of a human being. Human cloning requires the removal of genetic material (DNA) from the cells of one individual and introducing it into an egg, which is then coaxed into dividing, potentially producing an embryo. What is referred to as 'Reproductive cloning' implies that the egg is able to develop to a blastocyst, which is then implanted into the womb of a recipient mother who brings to term an individual genetically identical to the original donor. Recent successes in sheep, mice, cattle, and other mammals suggest that human cloning is an achievable goal [4], but predict that with current technology the vast majority of resulting embryos would be severely deformed. What has been termed 'therapeutic cloning' refers to the process of deriving ES cells from such blastocysts, which destroys the cloned human embryo before it develops beyond the blastocyst stage [3]. Reproductive and therapeutic cloning are not ethically distinct if one believes that human life, in a moral sense, begins at the first cell division (one cannot say the moment of conception in this case, since such embryos are not the union of a sperm and egg). Regardless, human cloning in any form is morally and scientifically distinct from producing ES cells from discarded IVF embryos that were created by the union of sperm and egg for non-research purposes.

THE PROMISE OF ES CELL RESEARCH

There are essentially three categories of medical promise from ES cell research. First, researching the requirements for ES cells to differentiate into various tissues will provide a wealth of valuable information about early human development. This information will shed light on diseases caused by events that happen very early in development, such as fetal alchohol syndrome, as well as birth defects due to chromosome abnormalities. ES cells also provide the potential to test drugs in freshly differentiated cells of different tissue types to more closely resemble the human condition. Currently, drugs are tested in either old cell lines that have been around for decades and are no longer representative of the tissue from which they came or in animal models. Hence, a lot can be gained from simply researching the cells, completely independent of the issue of therapeutic or reproductive cloning. But the most sensationalized and controversial hope for ES cell research is that, since they have the potential to make the cells for every tissue type, they provide a source of material from which to regenerate cells for any type of tissue replacement therapy, to treat individuals with diseases that cause degeneration of specific tissue types. This latter application is the one most closely aligned with therapeutic human cloning, which could produce ES cells that are genetically identical to the patient, alleviating the risk of immune rejection of the resulting tissue implant.

PUBLIC SUPPORT AND THE CURRENT POLICY IN AMERICA: RESEARCH ON EXISTING ES CELL LINES

Public support for research with ES cells necessarily implicates all taxpayers as interested parties in the ethical debate. This does not mean that government-sponsored research must have the support of every taxpayer, nor can legislation reflect the ethical opinions of every faction. However, it must have wide public ethical support, and it should balance the perceived needs of the public with a respect for the strong and sincere convictions of those in the minority. The current policy of the NIH, the main funding agency for research in the United States, makes a distinction between 'deriving' and 'using' ES cells [5]. The NIH supports research on existing ES cell lines that were already derived from discarded IVF embryos, with the uncompensated permission of the donors, using privately supported research funds, but does not support the derivation of new cell lines. In doing so, the current administration has postponed a decision as to the ethics of creating ES cell lines, either for research or for therapy.

While this decision has some merit in light of the complexity of the debate, it also reflects a failure of this administration to address a profound modern responsibility. Other countries, as well as privately funded entities, are forging ahead in a manner that may be less

thoroughly considered, and possibly riskier to the human condition. Coming to terms with this issue sooner rather than later, to establish sound policies for carefully regulated publicly funded research, empowers the public to combat irresponsible research. Arguably, even those who oppose such research might prefer it to be done under the auspices of government regulation, rather than allowing it to be subject to the whims of individuals. This is similar to the abortion issue, where many individuals who oppose abortion still support its legalization because it is preferable to forcing women to seek out illegal, unregulated, and unsafe procedures. The private sector is unlikely to divert funds solely for the purpose of researching ways to improve safety or alleviate ethical conflict, whereas public funding agencies can fill this gap. Furthermore, long-standing experience with all other cell lines, including ES cell lines derived from other species, indicates that the existing ES cell lines will lose their differentiation potential and the integrity of their genetic material as they are maintained in culture. It is likely that, within a matter of years, questions will arise as to the reliability of data obtained with these existing ES cell lines, which will make NIH funded research less competitive. As a results, the nation's best scientists will move their research overseas to more supportive environments. Finally, restricting ES cell research is tantamount to denying potentially life-saving therapy and brings with it the responsibility of any deaths that could potentially be avoided [6]. In short, there are serious costs to this decision not to decide. Hence, the current policy must be considered temporary and both scientists and ethicists should strive for a policy that will allow ES cell research to move into the realm of public funding, discussion, and monitoring.

THE NECESSARY NEXT STEP: AN ETHICAL FRAMEWORK FOR THE DERIVATION OF NEW ES CELL LINES

If publicly funded research is to seriously compete with the private sector in the advancement of ES cell research, there has to be a means to obtain new ES cell lines. In this section, I will argue that, so long as ES cells are derived from discarded IVF embryos, their derivation poses no greater ethical conflict than does existing policies that have already received wide public acceptance, namely, IVF and the parental donation of a dying child's tissue for medical research. For the purposes of this discussion, I will not re-visit the ethical conflicts that surround IVF or the issues of tissue ownership and the rights of parents to donate their child's tissue. Instead, I will begin with the premise that existing practices reflect the culmination of sound ethical debate and are consistent with modern medical ethics. This discussion also need not address the issue of exploitation of women via compensation to women for their oocytes or the related health issues for these donors, since any such compensation is done for IVF purposes and not for research purposes, and limits as to the number of such oocytes collected are dictated by considerations solely related to IVF, not to research. This is a reasonable position because discarded embryos from IVF provide a more than ample source of material for research, and restricting their derivation to such discarded embryos will ensure that excess embryos are not created for research purposes. I will, however, re-visit the issue of when an embryo becomes an individual, because strong ethical arguments for the derivation of ES cell lines can be made even with the most stringent assumption, that human life begins at conception.

IVF is now a common practice to allow couples to conceive a child when they would otherwise not be able to do so. Public policy and broad public support for this practice reflects the general sentiment that the ability to create and bring to term one life that would otherwise not exist outweighs the cost of losing many lives (discarded embryos) all of whom would also not otherwise exist. If we accept that these embryos, whom are to be discarded, are destined to be destroyed for sound ethical reasons, then the tissue derived from them deserves the same moral status as tissue derived from a deceased infant. In other words, human life is not sacrificed for research purposes (which have uncertain future good to society). In fact, the decision to put these embryos to death is made for reasons that have nothing to do with research, and the extraction of ES cell tissue is not performed until after this decision has been made.

Opponents will argue that, if one agrees that human life begins at conception, then the process of removing ICM from the 100 cell embryo causes its death and any process that accelerates the death of a human being is immoral. While this is true, I would argue that it is equally true for IVF. There are two important considerations here. First, does the 100 cell embryo deserve the same moral status as a fully developed or even partially developed human being? Clearly, the practice of IVF, which implies that many will die for one to live, already affords the 100 cell embryo a lower moral status. For example, if 300 IVF embryos had to be brought to the third trimester stage in order for a single one to be chosen, and the remaining 299 fully developed babies had to be destroyed, this would dramatically change the entire ethical landscape surrounding IVF. Second, once the decision has been made to put a human being to death for merciful reasons, the remaining question is the method of euthanasia. Euthanasia is defined as the act of inducing a painless death. Pain and suffering requires a nervous system, which is not present in any form at this stage of development, so there is no basis by which to argue that 'trophectoderm removal' is a non-humane method of euthanasia. In fact, I would argue that euthanasia by this means is a great deal more humane than allowing human embryos to be flushed down the sink or left to dry out in a medical waste bin. Once the embryo has been euthanized by 'trophectoderm removal', the decision to donate its tissue for research is, by accepted public policy, the decision of the parents. Once derived, ES cells have no potential to create a human being on their own, so their use in research poses no more ethical dilemma than research with other tissue cultures. Hence, one can still give the 100 cell embryo the profound moral respect that it deserves, and find sound moral reasoning for wrestling value from tragedy by salvaging ES tissue from a euthanized human embryo for potentially life saving research.

FUTURE IMPLICATIONS AND ULTIMATE GOALS OF ES CELL RESEARCH

Undoubtedly, there are decades of discovery before we will see the most sensational of medical benefits, transplantation of regenerated tissue into patients with degenerative diseases. In the meantime, the policy outlined above would allow research into early human development and birth defects, as well as the production of tissues for drug testing, to proceed. Nonetheless, it is irresponsible for scientists to ignore or deny the fact that ES cell research increases the temptation for therapeutic human cloning. As we become more sophisticated at differentiating ES cells, the limiting step in using this technology for transplantation therapy will be the immune rejection of tissues made from ES cells that are not genetically identical to the patient. Methodology for animal cloning will undoubtedly improve, and those individuals intent on developing human cloning in the private or international sector will inevitably work toward that goal. At a minimum, wealthy individuals will be seeking ways to create ES cells from themselves in order to have a genetically identical resource for replenishing their aging tissues. In this sense, policy that allows derivation and research on ES cells but restricts all types of human cloning is also a postponement of the inevitable. The technology for human cloning is coming, and it brings with it a whole new set of ethical dilemmas that are, however indirectly, an inextricable part of the ethics of ES cell research.

The issue of reproductive vs. therapeutic cloning is perhaps the easiest line to draw. While it is true that advances in therapeutic cloning will lead directly to technology for reproductive cloning, the latter can be easily distinguished from the former by outlawing the re-implantation of embryos into the womb, as the UK has done [7]. We have never let the fear of abuse stand in the way of progress. While knives, guns, poisons and the internet give the criminal mind additional tools and temptations with which to commit criminal acts, they do not necessitate such acts. With modern DNA analysis methods, any breech of such a clearly stated law would be easily detectable beyond any reasonable doubt.

Some would argue that, once cloning has created an embryo, bringing it to term is preferable to destroying it for the benefit of another individual. In fact, it could be argued that reproductive cloning for the purposes of creating life is far superior to therapeutic cloning with the intention of murdering the resulting individual. However, the mere thought of human reproductive cloning and the horror of the myriad malformed babies that would need to be born to produce each normal clone make this practice unacceptable worldwide. In fact, as this article is written, the U.S. stands in the way of an international ban on reproductive human cloning, because American policy does not distinguish therapeutic from reproductive cloning [8]. Since many countries advocate, indeed the UK has already formally permitted, therapeutic human cloning [9], this strong stance by the American government threatens to jeopardize international legislation that could prevent a practice that is considered abhorrent by the vast majority of the worlds population. In fact, a 2003 poll of 1, 012 Americans reveled that 67% favored allowing therapeutic cloning to proceed but only 12% favor reproductive cloning [10]. Hence, despite what some factions would argue, therapeutic and reproductive cloning are legally, scientifically and morally distinguishable and to deny this fact leads to extreme polarization of values and stagnates our ability to properly restrict the most objectionable of practices. Scientists and citizens alike stand on firm moral ground when they deny that research paving the way for therapeutic cloning necessarily gives way to the practice of reproductive cloning.

Nonetheless, there are still numerous moral conflicts to overcome with the issue of therapeutic cloning. Human cloning for the purposes of creating ES cell lines brings with it the additional ethical burden that the embryos were created and then euthanized solely for research purposes or for the benefit of another human being. This is clearly not 'wrestling value from tragedy' and so faces a higher bar for moral justification. Some would simply argue that the human embryo at the 100 cell stage does not command any moral value because it is not an individual at all. For example, some maintain that since the blatocyst can be 'twinned' (i.e. the cells can be separated to produce multiple embryos) it cannot be called an individual. Others would argue that a human being does not acquire individuality until it passes through certain developmental stages, or until that life can experience pain and suffering. Unfortunately, this developmental view of moral status is rather arbitrary, and conveniently allows too much room for adjustment to the particular research application. For example, does human life begin at gastrulation (the next step after the blastula), at neurulation (formation of a primitive streak, the first signs of nervous system development), at quickening (the first signs of movement), or at the moment of sentience (consciousness)? When can an embryo first feel pain or first suffer? Indeed, these are difficult questions. Somehow it seems inherently obvious that a wriggling fetus deserves more protection than a 100 cell embryo. Yet, the mere fact that an embryo has some capacity for development into a human being seems to endow it with a degree of moral respect not given simply to the pluripotent cells derived from it. The goal then should be to minimize the exploitation of human embryos at any stage of development.

Beyond these murky considerations lie other, somewhat more concrete ethical concerns. For example, due to the currently inefficient nature of the cloning process, the enormous number of anticipated technical hurdles, and the potential success of the method, an increased demand for oocytes will arise, raising issues of the exploitation of women across the world who will be paid or even coerced to donate eggs through procedures whose safety may be highly variable. Moreover, as the private sector weighs in, will therapeutic cloning be done with the best interests of embryo and patient alike, or will profit motives create a cost-benefit approach to cloning? Clearly these issues are on the horizon and they draw nearer as the potential for tissue regeneration increases through ES cell research. Hence, scientists must accept responsibility for therapeu-

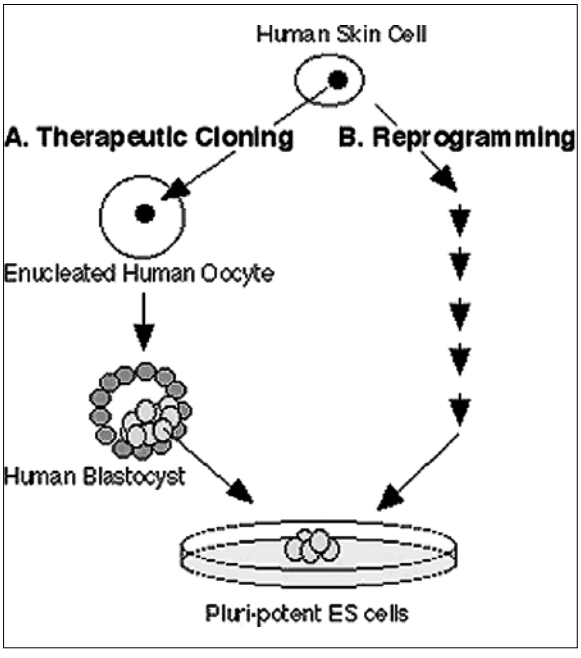

Figure 1. (**A**) In what is conventionally referred to as 'therapeutic human cloning', the nuclei from a patient's cells (e.g. skin cells) are injected into a human oocyte in which the nucleus has been removed (enucleated human oocyte). The patient's cells are hence 'cloned' as an embryo, which is allowed to develop into a human blastocyst (~100 cells). The 30–34 embryonic cells within this blastocyst can then be expanded into an embryonic stem (ES) cell line that can give rise to many human tissues (pluripotent). This type of technology is currently being used to clone animals, and is technically feasible in the near future for humans. The ethical conflict is that a human embryo must be created and then destroyed. (**B**) Although currently speculative, there are solid theoretical and experimental grounds to believe that adult cells can be coaxed into reverting to pluripotent ES cells by a step-wise process in which the cells would be exposed to factors that can reprogram them to return to the embryonic state. No human creation or destruction is involved in this strategy. Since this is a 'high risk' approach that will require substantial research to develop, public funding will be the only avenue in which to explore it's feasibility.

tic human (albeit, not reproductive cloning) if they are to participate in ES cell research.

Research As Part of the Solution

Fortunately, there is hope that research itself can find a way out of this dilemma. Straightforward issues of safety can be tackled by public funding into the risks involved in therapeutic cloning. Issues of female exploitation may be overcome by using animal eggs to re-program adult human cells. Even more promising is the possibility of being able to reprogram adult cells into stem cells, without the need for cloning (Figure 1 and [11,12]). Proof that this is possible comes from the simple fact that animal cloning is possible. If scientists can identify the factors that are able to de-differentiate adult cells back to the ES cell state, then there would be no need for eggs or embryos. Importantly, the private sector will never fund research into these and other alternatives because they constitute a long-term high-risk investment. This kind of basic research can only be funded through public mechanisms such as the NIH. Only by understanding how ES cells differentiate into various tissue types can we understand how to safely reverse the process. By making these kinds of alternative strategies practical and affordable the public will have the tools to combat degenerative diseases without having to resort to morally questionable practices. With this as the motivating factor, research into early human differentiation and de-differentiation can and should command broad ethical support

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