

Tremendous controversy has surrounded efforts to undertake research on totipotent human stem cells. To date public policy in the United States has attempted to skirt the ethical and social questions raised by this research. Annas *et al.* argue that research using human embryos as a source of totipotent stem cells can secure broad public support if there is an open and public discussion about the ethical justification for undertaking such research and the assurance of adequate federal regulation and oversight.

Stem cell politics, ethics and medical progress

Controversy over how to fund and regulate stem cell research continues in the US and is unlikely to be resolved anytime soon. The National Institutes of Health (NIH) has announced that it is prepared to fund stem cell research under yet-to-be-specified guidelines. The National Bioethics Advisory Commission (NBAC) issued a report on stem cells in mid-September, recommending that Congress change the law to permit the derivation and use of stem cells from embryos no longer needed for reproduction purposes that are stored at *in vitro* fertilization (IVF) clinics. The NBAC also recommended that the Department of Health and Human Services (DHHS) establish a new National Stem Cell Oversight and Review Panel to ensure that all federally funded stem cell research meets ethical standards. So far, the outgoing NIH director Harold Varmus has indicated that NIH will stick with its previous position and develop its own research guidelines. President Clinton seems to be in accord with Varmus, as is the American Association for the Advancement of Science. American politics surrounding embryo research, and any research relating to abortion, are complex and divisive. We believe it is time for a congressional debate on the funding, ethics and federal oversight of stem cell research. The NBAC report provides a useful opportunity for Congress to take this research seriously.

Political attention in the United States is focusing on stem cell research mainly because of two scientific reports^{1,2} and a November 1998 press release, all promising the potential of wide therapeutic applications if further research is actively pursued. Although ethical debate on stem cell research is in its infancy and should continue, federal law governing both stem cell research and federal funding and oversight of it needs to be clarified now. This is because the stakes are very high—stem cell research holds the promise of producing specialized, replacement cells to treat a variety of diseases and conditions, including parkinsonism, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis.

There are a variety of stem cells. Of most direct concern now are totipotent stem cells (capable of giving rise to an entire organism) and pluripotent stem cells (capable of giving rise to different kinds of cells, but not an entire organism). Totipotent stem cells exist in the very early embryo; pluripotent cells can be isolated from blastocysts, placental blood, bone marrow and fetal tissue. The reason stem cell research is politically controversial is the source of the stem cells. Whereas there is, for example, no controversy about research that uses stem cells derived from placental blood or bone marrow, the controversy relates exclusively to stem cells obtained either from human embryos or the reproductive tissues of aborted fetuses. Stem cell research is yet another chapter in America's long-running battle over the ethics of elective abor-

GEORGE J. ANNAS¹,
ARTHUR CAPLAN² &
SHERMAN ELIAS³

tion. There are many different ways to obtain human embryos to serve as the source for pluripotent and totipotent cells. University of Wisconsin scientists derived the stem cells immortalized from human embryos that were left over, 'spare' or 'orphan' embryos¹. These are human embryos that had been created in an IVF clinic for use in reproduction that were later donated by couples who no longer needed them or no longer wished to use them to have a child. Johns Hopkins University researchers derived their stem cells from primordial germ cells excised from the gonadal ridges and mesenteries of 5- to 9-week aborted fetuses². And University of Massachusetts researchers and Advanced Cell Technology claim to have created an embryo from an enucleated cow egg and human nuclear DNA that gave rise to stem cells. (The last claim has not been published in the scientific literature or otherwise substantiated.) Although often discussed in the same ethical breath, each of these sources of stem cells raises different legal and ethical problems.

Stem cells from human fetuses

One of the first actions President Clinton took upon becoming president in January 1993 was to lift the DHHS's moratorium on federal funding for research involving the transplantation of fetal tissue from induced abortions. He did so on the grounds that the moratorium "...has significantly hampered the development of possible treatments for individuals afflicted with serious diseases and disorders, such as Parkinson's disease, Alzheimer's disease, diabetes, and leukemia³." Current federal law continues to permit federal funding of research involving human fetal tissues, including stem cells, derived from dead fetuses, with three basic restrictions: There is a criminal prohibition against the sale of human fetal tissue for a price exceeding expenses of procuring and delivering it; informed consent is required if fetal tissue is to be used for therapeutic transplants; and finally, a prohibition exists on donating fetal tissue to a designated donee⁴.

Thus, under existing federal law, the federal government may fund research using stem cells derived from elective abortions of the type done by the Johns Hopkins researchers, at least if the research is done in states that do not prohibit it. The fight to prohibit the use of fetal tissues for research has been fought and lost in Congress, with the interests of the millions of Americans suffering from diseases that could possibly be ameliorated by such research taking precedence over ethical concerns about complicity in the practice of abortion itself or the moral status of the fetus. Arguments that would restrict such research to spontaneously aborted fetuses have been rejected on the basis that there is a biologic reason for such an abortion, such as infection or a genetic abnormality, both making the use of such tissue inappropriate^{3,5}.

Embryonic stem cells

The creation of embryos for the purpose of research has been ethically and politically contentious. Current law, for example, prohibits federal funding for the creation of a human embryo or embryos for research purposes; or for research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero* under 45 Code of Federal Regulations 46.208(a)(2) and section 498(b) of the Public Health Act⁶.

The term "human embryo or embryo" is defined as "any organism, not protected as a human subject...that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells⁶." Under this law, the NIH may not fund any research in which human embryos are created for research purposes, nor research in which any human embryos are destroyed. Thus, under existing law, the NIH could not fund the University of Wisconsin research.

We have previously suggested that the use of 'spare' or 'surplus' embryos from IVF clinics is ethically appropriate, mainly because they were created for procreative purposes that will no longer be fulfilled⁷. The creation of embryos for reproductive purposes with the consent of those providing their gametes is not ethically suspect. If it is granted that the moral standing of a frozen embryo derives more from its role in the context of human reproduction than in its physical properties⁷, then when a couple no longer wants them for procreation, they should be able to donate them for research. The choice of donating spare embryos for use in important medical research that cannot be done by other means is ethically superior to either destroying them or keeping them perpetually cryopreserved⁷.

The NIH, at least temporarily, has chosen not to ask Congress to reconsider or rewrite this ban. Instead, the NIH, on advice of counsel, has concluded that as pluripotent stem cells are not themselves "organisms" under the definition, NIH may fund research on such stem cells⁴. We agree with this as a narrow legal conclusion; but it raises the ethical question of where the embryos are obtained and the possibility of complicity in embryo destruction. In this regard, the NBAC has rightly rejected the NIH's position, noting "There is no compelling ethical justification for distinguishing between the derivation and use of human stem cells⁸."

But it is important to go further. Failure to explicitly address the ethics of using spare embryos as a source of stem cells not only invites continued political and ethical controversy and public disquiet but cedes the moral case to opponents of their use. Although the destruction of a human embryo is lamentable, there is a considerable moral difference between creating and destroying embryos solely to obtain stem cells and destroying unwanted human embryos that will never be used for reproductive purposes, to achieve benefit for those with serious diseases and disorders. The former involves the creation solely for the purpose of destruction whereas the latter involves salvaging something of value from a situation from which nothing else can be gained.

Embryos created by nuclear transfer

The use of human embryos created by transferring the nucleus of a somatic cell into an enucleated egg to produce stem cells cannot be federally funded if the research results in the destruction of the embryo. About a dozen states also regulate embryo

research to varying degrees⁹. We do not know what the Massachusetts researchers (from Advanced Cell Technology) actually did, but their 12 November 1998 press release states that the researchers "successfully developed a method for producing primitive human embryonic stem cells through nuclear transfer techniques (cloning)." Later, authors from Advanced Cell Technology went on to state "Several years ago, we transferred nuclei from human somatic cells (18 lymphocytes and 34 oral mucosal epithelial cells) into enucleated bovine oocytes to form a preimplantation embryo... of the 56 nuclear transfer units produced...only 1 reached the 16- to 400-cell stage¹⁰." Their claim, in other words, is that they created a human embryo using human DNA and the enucleated egg of a cow. Their press release promised, "We will not use this technology to clone human beings."

Many are troubled by the prospect of using human DNA to cross species boundaries. Mostly, concerns relate to attempts to create a whole organism, a human-animal hybrid. But there is also ample concern for safety even if the only goal is to create cells or tissues for human use. The long-term effect of using human nuclear chromosomes with shortened telomeres or cytoplasm containing animal mitochondrial DNA on the function and survival of newly created tissues remains uncertain. Safety concerns about this sort of genetic engineering must be taken very seriously.

It is especially disturbing that the only example of cross-species nuclear transfer has only been reported by press release. The protocol (if one existed) was not reviewed by the University of Massachusetts' local Institutional Review Board (IRB), even though state law which requires IRB review of this type of research. It is a crime in Massachusetts "...to use any live human fetus [which the statute defines as including "an embryo"] ...for scientific, laboratory, research or other kind of experimentation¹¹." Although the statute was not written with this type of research in mind, it applies to the creation of human embryos for research, and provides mechanisms such as prior review by IRBs, by which protocols that might run afoul of the law can be reviewed before they are initiated. The researchers, who were veterinarians and not physicians, may not have been aware of the ethical or legal dimensions of their research.

Federal policy and stem cell research

Advanced Cell Technology said it put out its press release to encourage debate about the ethics of what they had done. But this is not a reasonable course for provoking ethical debate. Ethics must be discussed before proceeding, not after the research is a *fait accompli*. Given the safety unknowns of mixing human nuclear DNA with bovine mitochondrial DNA, there is a powerful moral case against using this source of stem cells in human beings.

All research on totipotent and pluripotent stem cells in the US is now being done in the private sector without federal regulatory or ethical oversight. All three of the studies mentioned here were financed by private, for-profit biotechnology companies. Geron Corporation, which funded both of the two published studies, decided to set up its own ethics advisory board. The board's first statement, however, was not drafted until the research was complete and both papers had been accepted for publication¹². This seems more like 'ethical cover' rather than ethics that can be taken seriously, especially as the board rewrote their statement after the publication of the study's results.

The Geron ethics board repeated a phrase that often appears in discussions of the ethics of research involving the human embryo—that the embryo must be “treated with respect.” Despite its prominence in discussions of embryo and stem cell research, the phrase “treated with respect” borders on the trite. It is not clear what respect for an embryo means. Geron’s only real measure of respect is that the embryo be used “...with care only in research that incorporates substantive values such as reduction of human suffering¹².” The idea of respect is particularly jarring in the context of research that of necessity results in the destruction of the embryo. It is time to abandon this language in favor of an examination of whether or not the destruction of certain types of embryos can be justified in terms of the benefits to be produced through their use in research.

The Geron Ethics Board appropriately discussed informed consent, but remarkably (for an ethics board) approved a form provided to IVF patients to donate their embryos that states: “You will not benefit financially [from the research]...The cells derived in this study may be shared with Geron Corporation, located in Menlo Park, CA, as part of the study. Geron Corporation may benefit financially from the development and clinical use of the cells derived in this study¹².” The board describes this statement as “explicit” and “exemplary”, although it is almost certain that no IVF patient would know anything about Geron Corporation (other than where its corporate headquarters is located) or whether they want to make a personal donation to their for-profit research efforts. It is, in short, an inadequate level of disclosure.

Most saliently, Geron’s ethics board states as a final ethical principle that “all such research must be done in a context of concern for global justice.” The ethics board seems to recognize what few, if any, Geron stockholders would concede: If only the rich are likely to benefit from stem cell research, it should not be pursued at all as a matter of social justice. This principle follows from ideas of respect for embryonic and fetal tissue that permit its instrumental use only to “alleviate human suffering and to promote the health and well-being of human populations,” but obviously begs the question of whether for-profit corporations can ever have this as a realistic goal or how the company could be forced to adhere to this principle. As stated in the context of a policy that seems to have been created to provide an ethical rationalization rather than as an ethical guidance for research, it is not likely that it can or will be taken seriously.

Stem cell research ethics and the federal government

A decision by Congress not to fund an area of research at all, like research involving human embryos, simply leaves the private sector to make up its own rules (at least in the absence of a specific state law). As the drug market is driven by the goal of profit maximization, there is no obvious way for ethical or social justice considerations to become a part of corporate policy. If the federal government wants to actually influence how research is done on human embryos and fetal tissue, it must set forth clear and unequivocal rules that cover not just the research it funds, but all research, including privately financed research.

Debate at the federal level on embryo research has been pursued for more than 20 years with little to show for it other than driving most research into the hands of private corporations. This is unsatisfactory public policy for an area of research that has profound social policy implications. The oversight and reg-

ulation of stem cell research is too important to be left to private corporations. Rules for basic medical research involving fetal tissues and human embryos can and should be publicly developed and enforced at the federal level.

We think that research using human embryos can secure US public support if that support is accompanied by much more explicit and open federal regulation and oversight. A federal oversight panel, independent of the NIH and DHHS, should be created with authority to promulgate all regulations for research involving the use of human embryos, the authority to review and approve (or disapprove) all research projects in the US that use human embryos, as well as all research projects using stem cells and other cell lines derived from human embryos or aborted fetuses⁷. This oversight panel, which will have to be authorized by Congress, should be composed mainly of members of the public, but should also include scientific, medical, legal and ethical experts, as well as experts on religious doctrine. The panel must have sufficient funding and staff to undertake its duties. To have impact outside the US an international treaty is required. This would be a prudent course to follow.

All US research in any way related to abortion, including research on human embryos, has been held hostage to the politics of the American abortion debate^{3,7}, a debate that has not proven susceptible to political resolution. This does not mean that stem cell research must meet the same fate. The promise of stem cell research for millions of patients may afford an outcome in which the ethical debate can be resolved democratically in Congress. This opportunity to move from ethical gridlock to responsible ethical oversight of such research should not be missed. Our society can and should decide, through its Congress, what embryos should be used as sources of stem cells for research, what oversight must be in place in both the public and private sectors, and what limits should be placed on cross-species research.

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¹Health Law Department, Boston University School of Public Health
Boston, Massachusetts 02118, USA

²Center for Bioethics, University of Pennsylvania Medical Center
Philadelphia, Pennsylvania 19104, USA

³Department of Obstetrics and Gynecology, University of Illinois at Chicago
Chicago, Illinois 60612, USA