Stem Cell Research and Applications

Monitoring the Frontiers of Biomedical Research

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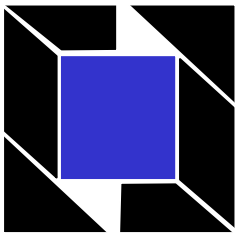

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The findings and recommendations of this report are endorsed by the Board of Directors of the American Association for the Advancement of Science and by the Institute for Civil Society as a contribution to public discussion of issues related to stem cell research and applications.

Preface

In the face of extraordinary advances in the prevention, diagnosis, and treatment of human diseases, devastating illnesses such as heart disease, diabetes, cancer, and diseases of the nervous system, such as Parkinson's Disease and Alzheimer's Disease, continue to deprive people of health, independence, and well-being. Research in human developmental biology has led to the discovery of human stem cells (precursor cells that can give rise to multiple tissue types), including embryonic stem (ES) cells, embryonic germ (EG) cells, and adult stem cells. Recently, techniques have been developed for the in vitro culture of stem cells, providing unprecedented opportunities for studying and understanding human embryology. As a result, scientists can now carry out experiments aimed at determining the mechanisms underlying the conversion of a single, undifferentiated cell, the fertilized egg, into the different cells comprising the organs and tissues of the human body. Although it is impossible to predict the outcomes, scientists and the public will gain immense new knowledge in the biology of human development that will likely hold remarkable potential for therapies and cures.

Derivation of ES cells from early human embryos, and EG and fetal stem cells from aborted, fetal tissues raise ethical, legal, religious, and policy questions. Further, the potential uses of stem cells for generating human tissues and, perhaps, organs, is a subject of ongoing public debate.

Taking all the above matters into account, the American Association for the Advancement of Science (AAAS) and the Institute for Civil Society (ICS) decided to undertake a study in order to propose recommendations for conducting stem cell research. To do so, we assembled a working group with broad expertise and diverse views to advise us and to assist with preparing a report. This study and the recommendations flowing from it were informed by the values of the members of this advisory group, the discussions that took place during a public meeting hosted by AAAS and ICS on August 25, 1999, as well as reports and recommendations of other groups in the United States and elsewhere that have reflected on the issues involved. These values include belief in the promotion of patient welfare and the social good, scientific freedom and responsibility, self-determination, encouragement of civic discourse, public accountability of scientists and research institutions, and respect for diverse religious, philosophical, and secular belief systems.

AAAS and ICS recognize that there are varied social, political, ethical, and religious viewpoints to be considered in discussions about the scientific use of tissue from human embryos and fetuses. Scientists do not presume to know all the answers and ramifications of basic research in human stem cells. Therefore, it is important to promote continued dialogue among all segments of society concerning the implications of stem cell research, and AAAS and ICS are committed to fostering an ongoing educational process that informs such public dialogue.

Findings and Recommendations

- **Human stem cell research holds enormous potential for contributing to our understanding of fundamental human biology. Although it is not possible to predict the outcomes from basic research, such studies will offer the real possibility for treatments and ultimately for cures for many diseases for which adequate therapies do not exist.**

The benefits to individuals and to society gained by the introduction of new drugs or medical technologies are difficult to estimate. The introductions of antibiotics and vaccines, for example, have dramatically increased life spans and improved the health of people all over the world. Despite these and other advances in the prevention and treatment of human diseases, devastating illnesses such as heart disease, diabetes, cancer, and diseases of the nervous system such as Alzheimer's disease present continuing challenges to the health and well-being of people everywhere. The science leading to the development of techniques for culturing human stem cells could lead to unprecedented treatments and even cures for these and other diseases.

As with all research, our ability even to contemplate the possibilities offered by stem cell-derived therapies is a result of many years of research. The science of stem cells dates to the mid-1960s, and many papers have been published on the isolation and laboratory manipulation of stem cells from animal models. While these models are imperfect, they are accepted in the scientific community as good initial predictors of what occurs in human beings.

There already exists evidence from animal studies that stem cells can be made to differentiate into cells of choice, and that these cells will act properly in their transplanted environment. In human beings, transplants of hematopoietic stem cells (the cells which eventually produce blood) following treatments for cancer, for example, have been done for years now. Further, somewhat cruder experiments (e.g., the transplantation of fetal tissue into the brains of Parkinson's patients) indicate that the expectation that stem cell therapies could provide robust treatments for many human diseases is a reasonable one. It is only through controlled scientific research that the true promise will be understood.

- **This research raises ethical and policy concerns, but these are not unique to stem cell research.**

Innovative research and new technologies derived from such research almost always raise ethical and policy concerns. In biomedical research, these issues include the ethical conduct of basic and clinical research as well as the equitable distribution of new therapies. These issues are relevant to discussions about stem cell research and its eventual applications; however, they are part of a constellation of ethical and policy concerns associated with all advances in biomedical research. Guidelines or policies for the use of human biological materials have been issued at many levels, from internal

review boards to the National Bioethics Advisory Commission, which recently released a detailed report on the use of such materials. Existing policies cover all aspects of research, from the use of cell lines in laboratories, to human subjects protections, that will surface in the consideration of stem cell research.

- **It is essential that there be a public that is educated and informed about the ethical and policy issues raised by stem cell research and its applications. Informed public discussion of these issues should be based on an understanding of the science associated with stem cell research, and it should involve a broad cross-section of society.**

It is essential for citizens to participate in a full and informed manner in public policy deliberations about the development and application of new technologies that are likely to have significant social impact. The understanding of the science is particularly important for discussing ethical and policy issues. Ideally, scientists should communicate the results of their research in ways that will be readily understandable to a diverse audience, and participate in public discussions related to stem cell research.

The ethical and policy issues raised by stem cell research are not unique, but this research has received a significant amount of public attention and there is much to gain by open reflection on the implications of this sensitive area of research. Congressional hearings, public meetings by government agencies, and media coverage have pushed stem cell research issues into a spotlight. There should be continued support for the open manner that has allowed all those interested to observe or participate in these processes and for a sustained dialogue among scientists, policy makers, ethicists, theologians, and the public to consider issues that emerge with the advancement of stem cell research.

- **Existing federal regulatory and professional control mechanisms, combined with informed public dialogue, provide a sufficient framework for oversight of human stem cell research.**

The appearance of new technology can evoke apprehension and engender uncertainty among segments of the population about its uses. Where these concerns are related to issues having important ethical and social implications, certain levels of oversight are appropriate. But it is important to create new oversight mechanisms or regulatory burdens only when there are compelling reasons for doing so.

Federal funding would automatically trigger a set of oversight mechanisms now in place to ensure that the conduct of biomedical research is consistent with broad social values and legal requirements. While basic laboratory research with personally non-identifiable stem cells does not pose special ethical or oversight challenges, an elaborate system of review is in place for research involving human subjects, ranging from procurement issues to the conduct of clinical trials. The Federal Common Rule governing human subjects research provides for local and federal agency review of research proposals in

such circumstances, weighing risks against benefits and requiring involved and voluntary consent. The Food and Drug Administration (FDA) has the authority to regulate the development and use of human stem cells that will be used as biological products, drugs, or medical devices to diagnose, treat or cure a disease or underlying condition. Further, states should adopt the Federal Government's *Model Program for the Certification of Embryo Laboratories*.

Complementing these regulatory mechanisms are the National Bioethics Advisory Commission (NBAC), which has demonstrated its legitimate claim to respect for its efforts as a national body to promote public input into social policy related to advances in biomedical research, and the Recombinant DNA Advisory Committee (RAC), which currently has a mandate to review the ethical and policy issues associated with gene therapy and could be authorized to change its mission to broaden its purview. These federal bodies should work with interested stakeholders in the conduct of stem cell research—professional organizations, patient disease groups, religious communities, the Congress, funding agencies and private foundations, industry, and others—so that the public can be assured that appropriate safeguards are in place as this research evolves.

Thus, at the present time, no new regulatory mechanisms are needed to ensure responsible social and professional control of stem cell research in the United States.

- **Federal funding for stem cell research is necessary in order to promote investment in this promising line of research, to encourage sound public policy, and to foster public confidence in the conduct of such research.**

Realizing the potential health benefits of stem cell technology will require a large and sustained investment in research. The federal government is the only realistic source for such an infusion of funds. For those who are challenged daily by serious diseases that could in the future be relieved by therapies gained through stem cell research, public funding holds the greatest promise for sooner rather than later research results that can be transferred from the bench to the bedside. Without the stimulus of public funding, new treatments could be substantially delayed.

The commitment of federal funds also offers a basis for public review, approval, and monitoring through well established oversight mechanisms that will promote the public's interest in ensuring that stem cell research is conducted in a way that is both scientifically rigorous and ethically proper. Additionally, public funding contributes to sound social policy by increasing the probability that the results of stem cell research will reflect broad social priorities that are unlikely to be considered if the research is carried out in the private sector alone.

There are segments of American society that disagree on moral grounds with using public monies to support certain types of stem cell research. However, public policy in a pluralistic society cannot resolve all the differences that arise in national debates on sensitive social issues. In the context of stem cell research, this leads to three practical

conclusions. One is a willingness to permit individuals, whether they are researchers or embryo or fetal tissue donors, to act in conformity with their own moral views on these matters. A second is the commitment to public involvement in research support when this research is related to the promotion and protection of public health, including the acquisition of new molecular and cellular insights into basic human developmental biology. A third is respect for opposing views, especially those based on religious grounds, to the extent that this is consistent with the protection and promotion of public health and safety.

- **Public and private research on human stem cells derived from all sources (embryonic, fetal, and adult) should be conducted in order to contribute to the rapidly advancing and changing scientific understanding of the potential of human stem cells from these various sources.**

There are three primary sources of stem cells, each with different characteristics as to how many different developmental paths they can follow and how much they can contribute to our understanding of a functioning organism. Embryonic stem cells (ES cells), derived from a very early embryo, and embryonic germ cells (EG cells), collected from fetal tissue at a somewhat later stage of development, have particular promise for a wide range of therapeutic applications because, according to our present knowledge, they are capable of giving rise to virtually any cell type. Research on these primordial cells will also provide a unique opportunity to study human cell biology.

Adult stem cells, obtained from mature tissues, differentiate into a narrower range of cell types. As a result, many cells of medical interest cannot currently be obtained from adult-derived stem cells. It is also less feasible to develop large-scale cultures from adult stem cells. However, it is important to note that, at this time, it is only adult human stem cells that are well-enough understood that they can be reliably differentiated into specific tissue types, and that have proceeded to clinical trials.

Because the study of human stem cells is at an early stage of development, it is difficult to predict outcomes and findings at this point in time. As more research takes place, the full developmental potential of different kinds of stem cells will become better understood.

In view of the moral concerns surrounding the uses of embryonic and fetal tissue voiced by a segment of the American population, strengthening federally and privately funded research into alternative sources and/or methods for the derivation of stem cells, including further initiatives on adult stem cells, should be encouraged. Human stem cell research can be conducted in a fully ethical manner, but it is true that the extraction of embryonic stem cells from the inner mass of blastocysts raises ethical questions for those who consider the intentional loss of embryonic life by intentional means to be morally wrong. Likewise, the derivation of embryonic germ cells from the gonadal tissue of aborted fetuses is problematic for those who oppose abortion. In contrast, adult stem cell research is more broadly acceptable to the American population.

- **Public funding should be provided for embryonic stem cell and embryonic germ cell research, but not at this time for activities involved in the isolation of embryonic stem cells, about which there remains continuing debate. This approach will allow publicly-funded researchers to move more quickly toward discoveries that will lead to alleviating the suffering caused by human disease.**

Although the derivation of human stem cells can be done in an ethical manner, there is enough objection to the process of deriving stem cells to consider recommending against its public funding. Further, for the foreseeable future there will be sufficient material isolated by researchers not using public funding that this exclusion will not have a negative impact on research.

There are many individuals who believe that any use of human embryos other than for achieving a pregnancy is unethical, believing that the embryo is a full human being from the earliest moments in the conception process. However, many religious traditions take a "developmental" view of personhood, believing that the early embryo or fetus only gradually becomes a full human being and thus may not be entitled to the same moral protections as it will later; others hold that while the embryo represents human life, that life may be taken for the sake of saving and preserving other lives in the future. The dialogue about these issues is ongoing in the United States, but these concerns need not exclude publicly-funded research activities on cell lines that have already been established.

- **Embryonic stem cells should be obtained from embryos remaining from infertility procedures after the embryo's progenitors have made a decision that they do not wish to preserve them. This decision should be explicitly renewed prior to securing the progenitors' consent to use the embryos in ES cell research.**

The most ethical source of human primordial stem cells is embryos produced for the process of in vitro fertilization whose progenitors have decided not to implant them and have given full and informed consent for the use of these embryos for research purposes. Two appropriate potential sources of donation are embryos with poor quality that makes them inappropriate for transfer and embryos remaining when couples have definitely completed their family and do not wish to donate the excess embryos to others.

Informed consent requires that the woman or couple, with substantial understanding and without controlling influences, authorize the use of their spare embryos for research purposes. Because assisted reproduction can be a stressful process, informed consent should be secured in two stages. The two-stage process would also maintain a separation between personnel working with the woman or couple who hope to get pregnant and personnel requesting embryos for stem cell research.

At the beginning of the process, personnel working with the woman or couple who hope to become pregnant should ascertain their preferences as to the future of embryos remaining after the assisted reproduction process. These options should include consent for embryo donation to another couple, consent for donation for research, and consent for destruction of the spare embryos. Once a couple has definitely decided that it has completed its family, then the couple should be approached a second time to secure an explicit consent to use the embryos in ES cell research.

- **Persons considering donating their excess embryos for research purposes should be afforded the highest standards of protection for the informed consent and voluntariness of their decision.**

Securing embryos for the purpose of harvesting stem cells must proceed in a careful fashion for several reasons. These are to protect the interests of the gamete donors, to reassure the public that important boundaries are not being overstepped, to enable those who are ethically uncomfortable with elements of this research to participate to the greatest extent possible, and to ensure the highest quality of research and outcomes possible.

Consonant with good research practice, policies on the procurement of embryos should include at least the following points: (1) Women should not undergo extra cycles of ovulation and retrieval in order to produce more "spare" embryos in the hope that some of them might eventually be donated for research; (2) Analogous with our current practice for organ donation, there should be a solid "wall" between personnel working with the woman or couple who hope to get pregnant, and personnel requesting embryos for stem cell purposes; (3) Women and men, as individuals or as couples, should not be paid to produce embryos, nor should they receive reduced fees for their infertility procedures for doing so; and (4) Consent of both gamete donors should be obtained.

- **Where appropriate, guidelines that can attract professional and public support for conducting stem cell research should be developed.**

At present, stem cell research raises no unique ethical or policy issues. As research advances issues may emerge that challenge acceptable ethical practices and public policy. Hence, there should be opportunities for public reconsideration of the need for guidelines specifically targeted to human stem cell research. Such efforts should be informed by the most current scientific evidence and should occur through a process that encourages broad involvement by all sectors of society.

Almost two decades of experience with the Recombinant DNA Advisory Committee's (RAC) oversight of recombinant DNA research suggest that the RAC could be an effective institutional focal point within the federal government to facilitate the type of public dialogue on stem cell research proposed here, and to coordinate efforts to develop new guidelines, where needed. The RAC has a proven track record of providing an open

forum for sorting out complex ethical issues and of defusing conflict. Furthermore, it has acquired a degree of legitimacy among scientists in both the public and private sectors, with its widely accepted *Points to Consider* in the design and conduct of gene therapy.

- **In order to allow persons who hold diverse moral positions on the status of the early embryo to participate in stem cell research to the greatest degree possible without compromising their principles, and also to foster sound science, stem cells (and stem cell lines) should be identified with respect to their original source.**

Patients and researchers should be able to avoid participating in stem cell use if the cells were derived in a way that they would consider to be unethical. As a matter of good scientific practice, records are routinely maintained on the sources of biological materials. It is of utmost importance that documentation of the original source of the stem cells can be made readily available to researchers and to potential recipients of stem cell therapies.

- **Special efforts should be made to promote equitable access to the benefits of stem cell research.**

The therapeutic potential for treating and possibly curing many serious diseases constitutes a major rationale for large-scale investments of public and private resources in human stem cell research. To justify funding stem cell research on the basis of its potential benefits, particularly the use of public resources, however, requires some assurance that people in need will have access to the therapies as they become available.

Several factors make it unlikely that there will be equitable access to the benefits of this research. Unlike other western democracies, the United States does not have a commitment to universal health care. More than 44 million people lack health insurance and therefore do not have reliable access even to basic health care. Others are underinsured. Moreover, if stem cell research were to result in highly technological and expensive therapies, health insurers might be reluctant to fund such treatments.

Overcoming these hurdles and assuring equitable access to the benefits of stem cell research in this country will be a politically and financially challenging task. It is therefore appropriate to begin considering how to do so now in advance of the development of applications. The federal government should consider ways to achieve equitable access to the benefits derived from stem cell research.

- **Intellectual property regimes for stem cell research should set conditions that do not restrict basic research or encumber future product development.**

The U.S. Patent and Trademark Office (PTO) has already stated that purified and isolated stem cell products and research tools meet the criteria for patentable subject matter. When research is funded by the private sector, as is currently the case with stem cell research, and is patented, it is a private matter whether and under what terms new intellectual property is obtainable for research purposes or development. This is of particular concern because the private sector will not invest resources in potential applications that they consider to lack commercial value, but that may have considerable therapeutic promise.

Given the promise of stem cell research, it is important to encourage the development of broadly beneficial therapeutic products with widespread access. This objective could be achieved in a variety of ways. Government investment in promising areas of research would enable federal agencies and laboratories to hold patents and to exercise them in ways that enhance development and contribute to the dissemination of this stem cell technology. Congress or the PTO should define a strong research exemption that would give third parties access to stem cell products and research tools for research purposes without having to obtain permission from the patent holder. Another possibility is to require compulsory licensing under limited and clearly defined circumstances.

- **The formation of company-based, independent ethics advisory boards should be encouraged in the private sector.**

Private sector research has played a crucial part in the advancement of research on stem cells. The leadership exhibited by the company that has sponsored all of the published human embryonic and germ cell research to date in establishing an external Ethics Advisory Board to develop guidelines for the ethical conduct of such research is laudable. While these private sector boards are not a substitute for public oversight and guidance, they can be a positive influence on the way that industry-funded stem cell research proceeds.

The credibility and impact of such ethics advisory boards will be enhanced if they review ethical issues at the start-up phase of the research, have multidisciplinary membership, including representatives from the local community, give minimum, if any, financial compensation for service, and share their own findings and recommendations with other companies. The latter provision could be especially helpful in developing a "case law" in the private sphere that would inform public efforts to develop national guidelines.

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The Science of Stem Cell Research and Potential Therapies

The benefits to society gained by the introduction of new drugs or medical technologies are considerable. The introductions of antibiotics and vaccines, for example, have dramatically increased life spans and improved the health of people all over the world. The science of stem cell therapies, potentially as important as these other advances, is about to enter a phase of research and development that could lead to unprecedented cures and palliative treatments. The current excitement over potential stem cell therapies emanates from new understandings of genetics and developmental biology. Although there is no way to predict the outcomes from basic research, there is enough data to indicate that much of the enthusiasm is warranted.

Current Status of Human Stem Cell Research

Overview

"Stem cells" is a term to describe precursor cells that can give rise to multiple tissue types. There are important distinctions, however, regarding how developmentally plastic these cells are; that is, how many different paths they can follow and to what portion of a functioning organism they can contribute. *Totipotent* stem cells are cells that can give rise to a fully functional organism as well as to every cell type of the body. *Pluripotent* stem cells are capable of giving rise to virtually any tissue type, but not to a functioning organism. *Multipotent* stem cells are more differentiated cells (that is, their possible lineages are less plastic/more determined) and thus can give rise only to a limited number of tissues. For example, a specific type of multipotent stem cell called a mesenchymal stem cell has been shown to produce bone, muscle, cartilage, fat, and other connective tissues.

There are many potential sources for stem cells. *Embryonic stem cells* are derived from the inner cell mass of a blastocyst (a very early embryo). *Embryonic germ cells* are collected from fetal tissue at a somewhat later stage of development (from a region called the *gonadal ridge),* and the cell types that they can develop into may be slightly limited. *Adult stem cells* are derived from mature tissue. Even after complete maturation of an organism, cells need to be replaced (a good example is blood, but this is true for muscle and other connective tissue as well, and may be true for at least some nervous system cells). Because these give rise to a limited number of cell types, they are perhaps more accurately referred to as multipotent stem cells, as discussed above.

Knowledge about stem cell science and potential applications has been accumulating for more than 30 years. In the 1960s, it was recognized that certain mouse cells had the capacity to form multiple tissue types, and the discovery of bona fide stem cells from mice occurred in 1971. Limited types of stem cell therapies are already in use. The most well-known therapy is the stem cell transplant (a form of a bone marrow transplant) for cancer patients. In this therapy, stem cells that can give rise to blood cells (red and white

cells, and platelets) are given to patients to restore tissue destroyed by high dose chemotherapy or radiation therapy. But it has been only recently that scientists have understood stem cells well enough to consider the possibilities of growing them outside the body for long periods of time. With that advance, rigorous experiments can be conducted, and the possibility of manipulating these cells in such a way that specific tissues can be grown is real. It is impossible to project when actual treatments or cures might emerge from such research, but the paths this research might take and potential applications have been much discussed. To understand the potential clinical applications, it is critical to understand the research that is taking place now.

Sources and Characteristics of Human Stem Cells

Human Embryonic Stem Cells. The study of human stem cells has barely begun and what is known is summarized in this section. The vast majority of experimental data discussed here are the results of experiments in mice. ES cells from the mouse have been intensely investigated since their discovery 18 years ago. Therefore, what is said about human ES cells assumes in part that their fundamental properties will resemble those of mouse ES cells. While on the surface this assumption appears to be reasonable it will have to be proven through intensive further investigation.

There is an abundance of stem cell lines from mammals including some from human beings. ES cells are valuable scientifically because they combine three properties not found together in other cell lines. First, they appear to replicate indefinitely without undergoing senescence (aging and death) or mutation of the genetic material. They are thus a large-scale and valuable source of cells. Second, ES cells appear genetically normal, both by a series of genetic tests and functionally as shown by the creation of mice with genomes derived entirely from ES cells. In mice these cells are developmentally totipotent; when inserted into an early embryo, they join the host cells to create a normal mouse, differentiating into every cell type of the body (it is this property that earns them the name "stem cell of the body"). ES cells can also differentiate into many cell types in tissue culture, including neurons, blood cells and cardiac and skeletal muscle. The normal embryo has about 100 cells with the properties of ES cells that exist for about one day and then develop into more advanced cell types. The isolation and subsequent growth of ES cells in culture allow scientists to obtain millions of these cells in a single tissue culture flask, making something once rare and precious now readily available to researchers. It is worth noting here the striking parallel to recombinant DNA and monoclonal antibody technologies, both of which have amplified rare and precious biological entities. Like those technologies, ES cell technology may well be transformative in opening scientific arenas that to date have been closed.

The isolation, culture, and partial characterization of stem cells isolated from human embryos was reported in November of 1998.[1] The ability of the cells to maintain their

[1] Thomson, J.A., Waknitz, M.A., Swiergiel, J.J., and Marshall, V.S., "Embryonic Stem Cell Lines Derived from Human Blastocysts." *Science, 282*: 1061-1062 (1998).

pluripotent character even after 4 to 5 months of culturing was demonstrated.[2] There is concern that this feature of these cells could also lead to cancerous growth. Thus far there are no data indicating the induction of malignant tumors, although there is some evidence for benign hyperproliferation (overgrowth of cells).[3]

Human Embryonic Germ Cells. Embryonic germ cells are derived from primordial germline cells in early fetal tissue during a narrow window of development. Unlike embryonic stem cells, animal experiments on embryonic germ cells have been limited. In November of 1998, the isolation, culture, and partial characterization of germ cells derived from the gonadal ridge of human tissue obtained from abortuses was reported.[4] These experiments showed that these EG cells are capable of forming the three germ layers that make all the specific organs of the body. There are fewer data from animal EG cell experiments than from ES cell experiments, but it is generally assumed that the range of potential fates will be relatively limited compared to ES cells, because the EG cells are much further along in development (5-9 weeks as opposed to 5 days in the published experiments). Fetal tissue may provide committed neural progenitors, but the feasibility of large scale sourcing and manufacturing of products utilizing such cells is questionable. Furthermore, the behavior of these cells *in vivo* is not well understood; significant research will be required to avoid unwanted outcomes, including ectopic tissue formation (additional, unwanted tissue), tumor induction, or other abnormal development.[5]

Human adult stem cells. From post-embryonic development through the normal life of any organism, certain tissues of the body require stem cells for normal turnover and repair. Stem cells that are found in developed tissue, regardless of the age of the organism at the time, are referred to as adult stem cells. The most well-known example of this are the hematopoietic stem cells of blood.[6] More recently, mesenchymal stem cells (MSC) required for the maintenance of bone, muscle, and other tissues have been

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[2] Definitions of "pluripotent" generally include the potential of the cell to form derivatives from all three germ layers. Traditionally, the layers and their derivatives are the endoderm (giving rise to the gut), the mesoderm (giving rise to cartilage, bone, and smooth and striated muscle), and ectoderm (giving rise to the nervous system and other epithelial tissue).

[3] Thomas Okarma (Geron Corporation), AAAS Public Forum on Stem Cell Research Issues (25 August 1999).

[4] Shamblott, M.J., Axelman, J., Wang, S., Bugg, E.M., Littlefield, J.W., Donovan, P.J., Blumenthal, P.D., Huggins, G.R., and Gearhart, J.D. "Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells. " *Proceedings of the National Academy of Sciences, 95*: 13726-13731 (1998).

[5] There is at least one report of abnormal development when the nuclei of mouse germ cells are transplanted into mouse oocytes. Kato, Y., Rideout, W.M., Hilton, K., Barton, S.C., Tsunoda, Y., and Surani, M.A. "Developmental potential of mouse primordial germ cells." *Development 126*: 1823-1832 (1999).

[6] There is a wealth of resources on the general topic of hematopoietic stem cells and their clinical uses. Because of the nature of primary and secondary diseases requiring hematopoietic stem cell transplant, the most comprehensive, up-to-date information can be found through one of the many National Cancer Institute-designated Comprehensive Cancer Centers. Particularly useful are http://oncolink.upenn.edu and http://www.fhcrc.org.

discovered.[7] Adult stem cells are multipotent; the number of tissues that they can regenerate compares poorly with the pluripotency of embryonic stem cells and embryonic germ cells. However, the MSC is in fact an excellent example of the potential for use of stem cells in human therapeutic procedures. MSCs are capable of differentiating into bone, cartilage, muscle, fat, and a few other tissue types. Their use for bone and cartilage replacement is undergoing FDA-approved clinical trials at the present time.

Adult-derived stem cell therapies will complement, but cannot replace, therapies that may be eventually obtained from ES cells. They do have some advantages. For example, adult stem cells offer the opportunity to utilize small samples of adult tissues to obtain an initial culture of a patient's own cells for expansion and subsequent implantation (this is called an autologous transplant). This process avoids any ethical or legal issues concerning sourcing, and also protects the patient from viral, bacterial, or other contamination from another individual. With proper manufacturing quality controls and testing, allogeneic adult stem cells (cells from a donor) may be practical as well. Already in clinical use are autologous and allogeneic transplants of hematopoietic stem cells that are isolated from mobilized peripheral blood or from bone marrow by positive selection with antibodies in commercial devices. In general, there is less ethical concern over their initial source. Additionally, since they normally differentiate into a narrower set of cell types, directing them to a desired fate is more straightforward. However, many cells of medical interest cannot, as of yet, be obtained from adult-derived cell types. Production of large numbers of these cells is much more difficult than is the case for ES cells. Based upon our present knowledge base, it appears unlikely that human adult stem cells alone will provide all of the necessary cell types required for the most clinically important areas of research.

The Clinical Potentials for Stem Cell Products

The economic and psychological tolls of chronic, degenerative, and acute diseases in the United States are enormous. It has been estimated that up to 128 million people suffer from such diseases; thus, virtually every citizen is effected directly or indirectly.[8] The total costs of treating diabetes, for example is approaching $100 billion in the United States alone.[9] As more research takes place, the developmental potential of different kinds of stem cells will become better understood. As the science is understood now, adult stem cells are limited in their potential to differentiate. Embryonic germ cells have a great differentiation capacity, and embryonic stem cells are thought to be able to differentiate into almost any tissue. Thus, different types of stem cells could have different applications. Below is a discussion of potential stem cell applications.

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[7] Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J., Moorman, M., Simonetti, D., Craig, S., and Marshak, D.R., "Multilineage Potential of Mesenchymal Stem Cells." *Science, 284*: 143-147 (1999).

[8] This approximation is based on aggregate counts from various sources compiled by the Alliance for Aging Research, Washington, DC.

[9] This number includes a "lost productivity" calculation, but does not include costs associated with diseases that are not classically secondary to diabetes, but are associated with immune system diseases generally. It is estimated that the true figure may be as high as $140 billion. See: http://www.diabetes.org/ada/c20f.asp.

Some Examples of Treatments for Major Diseases

Type 1 Diabetes in Children. Type 1 diabetes is an autoimmune disease characterized by destruction of insulin producing cells in the pancreas. Current efforts to treat these patients with human islet transplantation in an effort to restore insulin secretory function (obtained from human pancreas) are limited severely by the small numbers of donated pancreas available each year combined with the toxicity of immunosuppressive drug treatments required to prevent graft rejection.[10] Pluripotent stem cells, instructed to differentiate into a particular pancreatic cell called a beta cell, could overcome the shortage of therapeutically effective material to transplant. They also afford the opportunity to engineer such cells to effectively resist immune attack as well as graft rejection.

Nervous System Diseases. Many nervous system diseases result from loss of nerve cells. Mature nerve cells cannot divide to replace those that are lost. Thus, without a "new" source of functioning nerve tissue, no therapeutic possibilities exist. In Parkinson's disease, nerve cells that make the chemical dopamine die. In Alzheimer's disease, cells that are responsible for the production of certain neurotransmitters die. In amyotrophic lateral sclerosis, the motor nerve cells that activate muscles die. In spinal cord injury, brain trauma, and even stroke, many different types of cells are lost or die. In multiple sclerosis, glia, the cells that protect nerve fibers are lost.[11] Perhaps the only hope for treating such individuals comes from the potential to create new nerve tissue restoring function from pluripotent stem cells.

Remarkably, human clinical experiments have demonstrated the potential effectiveness of this approach to treatment. Parkinson's patients have been treated by surgical implantation of fetal cells into their brain with some benefit. Although not completely effective, perhaps owing to lack of sufficient numbers of dopamine secreting cells, similar experiments using appropriately differentiated stem cells should overcome those obstacles.[12] More complex experiments have already been successfully conducted in rodent models of Parkinson's.[13] Similar approaches could be developed to replace the dead or dysfunctional cells in cortical and hippocampal brain regions that are affected in patients with Alzheimer's.

Primary Immunodeficiency Diseases. Pluripotent stem cells could be used in treatment of virtually all primary immunodeficiency diseases. Presently, there are more than 70 different forms of congenital and inherited deficiencies of the immune system that have

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[10] These limitations are described in the summary of a beta cell replacement workshop: http://www.jdfcure.com/JDFINASAisletconfsummary.htm.
A paper describing the theory and limitations for use of islet cell transplantation, and including a comprehensive bibliography can be found at: http://www.islet.org/weir01.htm.

[11] http://www.mit.edu/afs/athena/user/p/a/pandre/www/Neurology.html.

[12] http://neurosurgery.mgh.harvard.edu/oisacson.htm.

[13] For example, see Schierle, G.S., Hansson, O., Leist, M., Nicotera, P., Widner, H., and Brundin, P., "Caspase Inhibition Reduces Aoptosis and Increases Survival of Nigral Transplants." *Nature Medicine 5*: 97-100 (1999).

been recognized. These are among the most complicated diseases to treat with the worst prognoses. Included here are diseases such as severe combined immunodeficiency disease (the "bubble boy" disease), Wiskott-Aldrich Syndrome, and the autoimmune disease lupus. The immune deficiencies suffered as a result of acquired immune deficiency syndrome (AIDS) following infection with the human immunodeficiency virus are also relevant here.[14] These diseases are characterized by an unusual susceptibility to infection and often associated with anemia, arthritis, diarrhea, and selected malignancies. However, the transplantation of stem cells reconstituted with the normal gene could result in restoration of immune function and effective normalization of life span and quality of life for these people.

Diseases of Bone and Cartilage. Stem cells, once appropriately differentiated, could correct many diseases and degenerative conditions in which bone or cartilage cells are deficient in numbers or defective in function. This holds promise for treatment of genetic disorders such as osteogenesis imperfecta and chondrodysplasias. Similarly, cells could be cultivated and introduced into damaged areas of joint cartilage in cases of osteoarthritis or into large gaps in bone from fractures or surgery.

Cancer. At the present time, bone marrow stem cells, representing a more committed stem cell, are used to rescue patients following high dose chemotherapy. Unfortunately, these recovered cells are limited in their capacity to restore immune function completely in this setting. It is hoped that injections of properly-differentiated stem cells would return the complete repertoire of immune response to patients undergoing bone marrow transplantation. Complete and functional restoration will be required if, for example, immune/vaccine anticancer therapy is to work. More importantly, success would permit use of very toxic (and effective) chemotherapeutic regimens that could not currently be utilized for lack of an ability to restore marrow and immune function.

Uses in Research

Much is left to be discovered and understood in all aspects of human biology. What has been frequently lacking are the tools necessary to make the initial discoveries, or to apply the knowledge of discoveries to the understanding of complex systems. These are some of the larger problems in basic and clinical biology where the use of stem cells might be the key to understanding.

A new window on human developmental biology. The study of human developmental biology is particularly constrained by practical and ethical limitations. Human ES cells may allow scientists to investigate how early human cells become committed to the major lineages of the body; how these lineages lay down the rudiments of the body's tissues and organs**;** and how cells within these rudiments differentiate to form the myriad functional cell types which underlie normal function in the adult. The knowledge gained will impact many fields. For example, cancer biology will reap an especially large reward because it

[14] http://www.niaid.nih.gov/publications/pid/contents.htm.
http://www.nih.gov/grants/guide/1997/97.03.21/rfp-rfa-primary-immu11.html.

is now understood that many cancers arise by perturbations of normal developmental processes. The availability of human ES cells will also greatly accelerate the understanding of the causes of birth defects and thus lead directly to their possible prevention.

Models of human disease that are constrained by current animal and cell culture models. Investigation of a number of human diseases is severely constrained by a lack of *in vitro* models. A number of pathogenic viruses including human immunodeficiency virus and hepatitis C virus grow only in human or chimpanzee cells. ES cells might provide cell and tissue types that will greatly accelerate investigation into these and other viral diseases. Current animal models of neurodegenerative diseases such as Alzheimer's disease give only a very partial representation of the disease's process.

Transplantation. Pluripotent stem cells could be used to create an unlimited supply of cells, tissues, or even organs that could be used to restore function without the requirement for toxic immunosuppression and without regard to tissue matching compatibility. Such cells, when used in transplantation therapies, would in effect be suitable for "universal" donation. Bone marrow transplantation, a difficult and expensive procedure associated with significant hazards, could become safe, cost effective, and be available for treating a wide range of clinical disorders, including aplastic anemia and certain inherited blood disorders. This would be especially important in persons who lost marrow function from toxic exposure, for example to radiation or toxic agents. Growth and transplant of other tissues lost to disease or accident, for example, skin, heart, nervous system components, and other major organs, are foreseeable.

Gene Therapy. In gene therapy, genetic material that provides a missing or necessary protein, or causes a clinically-relevant biochemical process, is introduced into an organ for a therapeutic effect. For gene-based therapies (specifically, those using DNA sequences), it is critical that the desired gene be introduced into organ stem cells in order to achieve long-term expression and therapeutic effect. Although techniques for delivering the therapeutic DNA have been greatly improved since the first gene therapy protocol almost 10 years ago, there are as yet no bona fide successes. Besides delivery problems, loss of expression or insufficient expression is an important limiting factor in successful application of gene therapy and could be overcome by transferring genes into stem cells (which presumably will then differentiate and target correctly).

Spiritual and Religious Contexts

Two broad and somewhat opposing themes characterize the response of most religious communities and traditions to the promising new biomedical technology that stem cell research represents. On the one hand, there is a moral commitment to healing and to relieving suffering caused by injury and illness. For biblically-based traditions, this commitment reflects a responsibility to serve as partners with God and stewards of God's creation. Because of this commitment, most religious communities applaud the promise of stem cell research for enhancing scientific understanding of human development; for probing the cellular origins of cancer, diabetes, spinal cord injury, arthritis, and a host of other lethal or disabling illnesses and conditions; for developing more effective pharmacological drugs; and for pursuing successful tissue and organ transplant technology.

On the other hand, most traditions also warn that human beings are not God. Humans lack omniscience and our pursuits are often tainted by selfishness. With regard to stem cell research, this suggests the need to be cautious in pursuing the promise of this research and to strive to anticipate and minimize its potential harms and misuses. These include direct harms to the donors of the tissues and embryos from which stem cells may be derived and harms to future research subjects exposed to the unknown risks of stem cell implants. It also includes possible longer-term harms to society ranging from damage to our respect for the sanctity of human life to inequities resulting from the appropriation or privatization of a resource with great potential to benefit everyone.

Beyond these two broadly shared themes, there is significant disagreement among American religious communities over some of the specific moral issues raised by stem cell research. The most medically promising stem cells, with a capacity to differentiate into any of the human body's cell types, are derived either from the inner cell mass of preimplantation embryos (ES cells) or from the gonadal tissue of aborted fetuses (EG cells). Both of these sources involve extraction and manipulation of cells from human embryos or fetuses. This raises issues of fundamental importance for some religious communities and can profoundly engage the conscience of Americans.

There are two principal areas of disagreement. One concerns the question of whether it is ever morally appropriate to destroy an embryo and whether the benefits of research provide a justification for doing so. At issue here is the question of whether the human embryo (or fetus in the case of EG cells) possesses significant moral status and must be protected from harm. Among those who answer this in the affirmative, a second question and some further disagreements arise. This is the question of whether researchers who have played no part in the destruction of an embryo or fetus may ethically utilize cellular materials produced in these ways. This is the question of when, if ever, it is morally permissible to cooperate with or benefit from what some persons regard as evil acts.

The first of these questions is among the most controversial in our society. Some religious communities believe the embryo or fetus is a full human being from the moment of conception, since it is genetically human and has the potential for development into a

human individual.[15] Other traditions take a "developmental" view of personhood, believing that the early embryo or fetus only gradually becomes a full human being and thus may not be entitled to the same moral protections as it will later.[16] Still others hold that while the embryo represents human life, that life may be taken for the sake of saving and preserving other lives in the future.[17]

It is noteworthy that, despite these differences, all these positions can support research that does not involve the use of embryonic or fetal cells, that is to say, adult stem cell research. Opponents of abortion also support the use of fetal tissues when these result from stillbirths or miscarriages. They object only to the deliberate destruction of fetuses or embryos. Unfortunately, these zones of agreement do not include some promising areas of stem cell research, those involving the use of cells obtained from embryos (ES cells), or from deliberately aborted fetuses (EG cells). The fact that much basic research needs to be done in the area of human embryonic development suggests that both ES and EG cells will continue to play an important role in future research endeavors. Where germ cells are concerned, spontaneous abortions or stillbirths are a poor source of the tissue, both because the collection of the tissue requires substantial preparation, the critical time period is of short duration, and because, with spontaneous abortions particularly, this tissue is likely to suffer from genetic abnormalities. While continuing research efforts must be made to understand the biology of alternative sources of such cells, adult stem cells cannot entirely replace either EG and ES cells because much basic research needs to be done in the area of early human embryonic development for which EG and ES cells are required.

The zone of agreement is somewhat widened, however, when we recognize that some who adamantly oppose the destruction of embryos or fetuses can accept the view that research on the cellular materials remaining from such acts is not always unethical. These individuals take the view that not all acts benefiting from others' wrongdoing are morally impermissible, so long as one is not in any way involved in the wrongdoing and one's own acts do not foster, encourage, or lend support to it. For some who hold this moral position, no involvement with fetal or embryo destruction can meet this test, as all such

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[15] **"**Donum Vitae" (Respect for Human Life), *Origins* 16: 697-711 (1987); Doerflinger, R., "Destructive Stem-Cell Research on Human Embryos." *Origins* 28: 769-73 (April 29, 1999); Grisez, G., "When Do People Begin?" *Proceedings from the American Philosophical Association*, 63 (1990).

[16] This position includes a number of Catholic moral theologians; see, for example, Shannon, T.A., and Walter, A.B., "Reflections on the Moral Status of the Pre-Embryo." *Theological Studies* 51: 603-26 (1990); Cahill, L. S., "The Embryo and the Fetus: New Moral Contexts." *Theological Studies* 54: 124-42 (1993). Most mainline Protestants hold a developmental view; see, for example, Peters, T., *For the Love of Children.* pp.96-100. (Louisville, KY: Westminster, John Knox Press, 1996). In Jewish tradition, while not "mere tissue," the fetus prior to forty days development is categorized differently than it would be later. Siegel, S., "Fetal Experimentation" in *Contemporary Jewish Ethics* (Kellner, M., ed.) *289* (1978).

[17] Robertson, J., "Symbolic Issues in Embryo Research," *Hastings Center Report* 25 1: 37-38 (January-February 1995).

involvement amounts to wrongful cooperation with evil.[18] However, others equally opposed to embryo destruction may conclude differently.[19]

Despite the possibility of achieving some consensus in these directions, important disagreements remain. Some who hold the view that full moral protection begins at conception will conclude that their religious and ethical perspective requires them to oppose any federal involvement in stem cell research so long as embryo or fetal destruction is involved, and they may even believe that all activities of this sort should be prohibited. Others, drawing on their own religious beliefs, will determine that stem cell research is not only ethically permitted, but required in the name of promoting human health.

[18] Smith, R.E., "The Principle of Cooperation in Catholic Thought." *The Fetal Tissue Issue: Medical and Ethical Aspects*, pp. 81-92. (Braintree, MA: Pope John Center, 1994).

[19] Ibid., pp. 90-92. Smith observes that only in cases where the researcher is intentionally and proximately involved in performing abortion is the prohibition against cooperating with evil absolute. In other cases, a negative judgment results from a difficult balancing of benefit and harm. Presumably in such cases individuals who share an opposition to abortion or embryo destruction may conscientiously balance things differently and come to different conclusions regarding the possibilities of cooperation.

Ethical Concerns

The Moral Status of Human Stem Cells

Human embryonic germ (EG) cells are derived from the gonadal ridge tissue of an aborted fetus within five to eight weeks after conception. The procedure is analogous to the harvesting of organs from a cadaver. Here the ethical issue is not so much the status of the aborted fetus, but whether those who consider abortion an illicit act, despite its legality, can participate in the research on tissues so derived.

The ethical status of human embryonic stem cells partly hinges on the question of whether they should be characterized as embryos or specialized bodily tissue. Although the answer to this question will be less important to those who believe that the early embryo has little or no moral status, it will shape the views of those who regard the embryo as significantly protectable.

One way of approaching this question is by looking first at ways in which the embryo has been understood. In the context of the abortion and human embryo research debates, a series of criteria has been proposed to determine the moral status of the pre-implanation human embryo. Among these are an entity's possession of a full human genome; its potential for development into a human being; sentience; and the presence of well-developed cognitive abilities such as consciousness, reasoning ability, or the possession of self-concept. Those taking the position that the early embryo has full moral status (equal to that of any child or adult human being) usually stress the first two of these criteria: possession of a unique human genome *and* the potential for development into a human being are regarded as sufficient for ascribing full moral status to it.

Since most cells in the human body possess a unique diploid genome and are not regarded as morally protectable, the question of whether ES cells are morally equivalent to somatic cells or whether they are more like human embryos largely hinges on an understanding of stem cells' potentiality. Here the matter calls for further refinement since, as developments in mammalian cloning technology suggest, any human cell (or tissue) may have the potential to become a person. To avoid this problem, potentiality arguments typically appeal to some consideration of normal or natural processes: embryos have a natural potentiality to become a person in that the natural development of an embryo, unlike tissue, is to become a human being. Of course, the interpretation and significance of the word "natural" is controversial.

Can we conclude that stem cells have equivalent moral status because of their potential to become a human being? Since potentiality is being understood here as "natural potentiality," determining the moral status of a stem cell rests in part on whether its potential to become a person is natural, as it is with embryos, or contrived, as it would be with cells that are cloned. Being natural or contrived does not refer to the ease or facility of the process or the need for technological intervention. Regardless of how cloning technology may develop, for example, it will not be seen as a natural process by those who hold that

embryos have a natural potential to become a full human being. To fail to distinguish between the natural and contrived development of the embryo would otherwise, among other things, unreasonably commit us to the full moral protection of every human cell.

The potential of a stem cell to become a human being seems to be much more like that of a somatic cell that could be cloned than like an embryo. The natural development of the individual cells of the embryonic disk (from which stem cells are derived) is to become parts of a human being. Isolated from the total structure of the embryo or blastocyst, these cells, even under favorable growth conditions, will not develop the trophoblast (the outer layer of cells of the embryo) or other structures needed for continued development. Another way of putting this is to say that stem cells are pluripotent rather than totipotent. It is true that advanced technology might be able to render these cells effectively (if not actually) totipotent. Research undertaken in Canada in 1993 involving the aggregation of mouse stem cells with a genetically manipulated embryo led to the cells' subsequent growth and population of the entire organism.[20] However, such manipulations are arguably even less "natural" than is current cloning technology. Insofar as potentiality considerations alone are concerned, therefore, stem cells would not seem to have the same moral status as embryos**.** For those following this line of reasoning, including those who accord significant moral status to the embryo, stem cells may thus be regarded and treated as any other form of human bodily tissue.

Potentiality is a complex idea, drawing on even more complex and undeveloped notions of "nature" and "the natural." Rather than entirely clarifying these matters, biology complicates them by indicating the developmental continuum always present in human growth and maturation. Continuing discussion will be needed involving the many viewpoints around the question about how we can best protect the multiple values evoked by research at life's beginnings. These include values such as our commitment to the protection of human life generally, the promotion of human health, and respect for the views of others in a civil, democratic society.

Moral Issues Surrounding the Sources of Stem Cells

At present, there are three possible sources of stem cells: adult stem cells derived from pediatric or adult donors; embryo germ cell stem cells (EG cells) derived from aborted fetuses; and embryonic stem cells (ES cells) derived from disaggregated preimplantation embryos. The first of these sources poses no special ethical problems for the majority of people. Adults and children can donate tissue so long as the appropriate conditions of consent are respected. Individuals who do not object to induced abortion will be less concerned about the use of EG cells than those opposed to abortion.

The least ethically problematic case would be to harvest stem cells from spontaneously aborted fetuses. There are, however, several obstacles to obtaining useful EG cells from

[20] Nagy, A., Rossant, J., Nagy, R., Abromow-Newerly, W., and Roder, J.C., "Derivation of Completely Cell Culture-Derived Mice from Early-Passage Embryonic Stem Cells." *Proceedings of the National Academy of Sciences* 90: 8424-8428 (1993).

spontaneously aborted tissue. Foremost is the problem of the harvesting healthy cells from fetuses. For the foreseeable future, extracting and culturing stem cells will be more of an art than an established technology. The amount of material that can be derived this way is limited even under the best circumstances.[21] Results from several studies indicate that about 60% of all spontaneous abortions arise as a result of specific fetal anomalies; specific chromosomal abnormalities were identified in about 20% of those.[22] While stem cells with damaged genetic complements may be useful for a limited number of experiments, they are unlikely to be the basis of experiments leading to useful "normal" tissue. Finally, there is the matter of timing. EG cells can only be obtained during a narrow developmental phase, within the first eight weeks after conception. Most spontaneous abortions that occur during this period do not take place in a hospital or clinic where the tissue can be readily obtained.

Those who do not accord significant moral weight to the pre-implantation embryo will probably not object to its being destroyed to be used as a source of ES cells. Some people holding this view may also accept the deliberate creation of embryos for this purpose, while others would only permit the use of so-called "spare embryos" remaining from infertility procedures.

The second and third source noted above (i.e., embryonic stem cells or embryonic germ cells obtained from elective abortions), however, raise special moral questions for those who regard either abortion or the destruction of early embryonic life as morally wrong. Can such people support or become involved in research using EG or ES cells when these cells are derived from what they regard as the morally unacceptable killing of a fetus or embryo? This raises the question of "complicity" or "cooperation" with evil. In the past, this issue has sometimes been discussed by Roman Catholic thinkers in connection with the issue of fetal tissue research.[23]

What constitutes morally wrongful cooperation with evil deeds? It is clear that not all use of goods produced by wrongful acts is immoral. For example, medical researchers routinely employ tissues of people who are victims of murder or other wrongful acts. At what point does use become "cooperation" or "complicity"? In answer to this, philosophers have focused on four different ways that could make one guilty of cooperation with evil. First, there is actual, direct involvement in the wrongful deed, as when a researcher administers the lethal dose to an innocent victim in order to secure tissue samples. Second, there is direct encouragement to such by the researcher, as when

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[21] In Testimony before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, John Gearhart discussed in general how his laboratory collected tissue from therapeutic abortions. Testimony on Stem Cell Research, 2 December 1998. http://www.senate.gov/~appropriations/labor/test.htm.

[22] Boue J., Boue A., Lazar p., " Retrospective and Prospective Epidemiological Studies of 1500 Karyotyped Spontaneous Human Abortions." *Teratology,* 12:11-26 (1995).

Simpson J.L., Bombard A., "Chromosomal Abnormalities in Spontaneous Abortion: Frequency, Pathology and Genetic Counseling." In: Bennett MJ, Edmonds DK, eds. *Spontaneous and Recurrent Abortion.* Oxford: Blackwell Scientific Publications 51-76. 1987.

Craver R.D., Kalousek D.K., "Cytogenetic Abnormalities Among Spontaneously Aborted Previable Fetuses." *American Journal of Medical Genetics Supplement, 3*:113-119 (1987).

[23] Smith, R.E., "The Principle of Cooperation in Catholic Thought."

researchers encourage others to kill prisoners or concentration camp inmates in order to ensure themselves a supply of research material. Third, there is indirect encouragement to wrongful killing by performing research whose beneficial consequences lead to wider acceptance of the wrongful practices and their perpetuation. Fourth, even when encouragement is not an issue, there is the appearance of endorsing, conferring legitimacy on, or diluting the condemnation of the wrongful deed.

It may be possible for stem cell research using embryonic tissues to be conducted in ways that many people otherwise opposed to embryo destruction would regard as morally acceptable. To some extent this is already the case in the area of fetal tissue research. Careful regulatory requirements that insulate researchers from direct involvement with abortion and the recognition that abortion decisions made by women both are and should be separated from permission to use the fetus's tissues in research have reduced opposition to the current practice of federally funded fetal tissue research. One sign of this is the tendency by some who are concerned with ES research to believe that EG stem cell research using fetal tissue poses fewer questions than does ES cell research, where deliberate embryo destruction by the researcher is viewed as a first step in the process.[24]

Properly conducted and regulated ES cell research may pose fewer ethical questions than EG cell research. But future ES researchers need not be involved in this way. Each year, thousands of embryos are routinely destroyed in infertility clinics around the world. In Great Britain, this is legally mandated. Procedures established there by the Human Fertilization and Embryology Authority require that frozen embryos not used within a set period time to establish a pregnancy must be destroyed.[25] In 1996, over 3000 such frozen embryos were mandatorily discarded. In the United States, contractual agreements between couples using infertility services and clinics providing these services could lead to a similar outcome. Estimates as to the number of embryos that are untransferable or "abandoned" range up to 100,000. Some patients may donate their embryos to other infertile people, and some may choose to keep the embryos frozen permanently. But prior to commencing an infertility procedure, couples are generally asked to agree to the disposition of unused embryo. Many clinics specifically note in their agreements that "excess" embryos can be donated to research, can be destroyed, can be donated to other infertile couples, or can be cryopreserved permanently.

These facts make the separation of the decision to destroy an embryo and the decision to donate it for research even greater than is the case in fetal tissue research. The possible use of fetal tissue in research must be raised with a woman who is actively involved in making an abortion decision. Although there is little evidence that a woman's decision is influenced by the beneficial prospects of research, this is enough of a possibility to trouble those who fear that such research will encourage abortion. No such proximate involvement is needed for ES cell research. At the time they are involved in an infertility procedure, individuals or couples usually make a decision about what is eventually to be

[24] This appears to be a line of reasoning in the NBAC report. See National Bioethics Advisory Commission, "Ethical Issues in Human Stem Cell Research: Executive Summary," September 1999. Available at: http://bioethics.gov/stemcell_exec_intro.htm.
[25] http://www.hfea.gov.co.uk.

done with their unused frozen embryos. A decision to destroy these embryos can thus be separated by months or years from the subsequent decision to donate such embryos for research purposes. When the clinic is at the point of destroying an embryo, the progenitors commitment to this course can be reascertained and, following that, their informed consent to its possible use in research can be secured.[26]

Workers in clinics or others who disaggregate embryos in order to prepare immortalized ES cell lines may be accused of wrongful conduct by those who oppose embryos' destruction. However, researchers further down the line who merely employ these tissues in beneficial research would seem to be less subject to this accusation. A further concern for these researchers and public agencies who fund their activities is whether the broad social benefits accruing from ES cell research will have the effect of endorsing, conferring legitimacy on, or diluting the condemnation of the practice of destroying embryos in infertility medicine. But there is little reason to believe that this will be the case. For the foreseeable future, many individuals and couples will use infertility procedures to have children. Until the remote point is reached when these procedures attain a level of 100 per cent efficiency (requiring the creation of only one embryo for each birth), spare frozen embryos will be in existence, some of which will eventually have to be destroyed. This will remain true regardless of the benefits of ES cell research. There is no reason to believe that the possibility of stem cell research will have any impact on the actual thinking or decisions of people seeking to have a child by these means. In view of this, the conclusion that researchers who receive ES cells produced in these ways do not cooperate with, condone or encourage embryo destruction is a reasonable one. Of course, some researchers may disagree and refuse to utilize ES cell lines as a sign of their moral opposition to anything related to the destruction of embryos. However, other researchers equally opposed to embryo destruction may conclude that the use of already existing stem cell lines is not itself morally objectionable. Indeed, in view of the probability of the eventual destruction of substantial numbers of embryos in connection with infertility procedures, it can be argued that ES cell research is a way of producing some benefit from what would otherwise be regarded as a situation of loss. In any case, the link between ES research and wrongful acts here is remote enough to permit public funding of this research.

There are several implications of these ideas relevant to the future conduct and possible public funding of ES research. In order to minimize the assault on many citizens' moral convictions, ES cell lines should be established using embryos remaining from infertility procedures whose progenitors have independently made a decision that they do not wish to preserve them. Whenever possible, this determination should be explicitly renewed prior to securing the progenitors' consent to use the embryos in ES cell research. As much as possible, an effort should be made to separate ES cell research—and researchers—from the manipulation or destruction of embryos, and public funds should not be directly used to support the destruction of embryos to produce ES cell lines.

[26] The requirement of consent for the use of an embryo in research is consistent with all tissue donation procedures and does not in itself constitute either an inducement to destroy the embryo or undue complicity in the progenitors' decisions. For a fuller discussion of this matter in relation to fetal tissue research, see *Report of the Human Fetal Tissue Transplantation Research Panel*, December 1988:4-5.

Sources of Stem Cells and Guidelines for Use

Securing stem cells for research, whether from children, adults, aborted fetuses, or embryos, must be done under conditions of the most rigorous integrity for several reasons. These are to protect the interests of the donors, to reassure the public that important boundaries are not being overstepped, to enable those who are ethically uncomfortable with elements of this research to participate to the greatest extent possible, and to assure the highest quality of research and outcomes.

As already noted, there are three different types of stem cells, derived from three different sources. Obtaining the first type, adult stem cells, presents no new ethical problems. Whether from adults or from children, protection of donors comes under the heading of research with human subjects, where adequate protection and regulation exist.

The second source is cells derived from aborted fetuses. Research with fetal tissue of all types is already ongoing in both the private and public sectors. Current federal regulations that clearly separate the woman's decision to have an abortion from her decision to donate tissue[27] from the aborted fetus appear adequate to cover the situation of fetal stem cells as well, because the issues are the same.

The third source, pre-implantation embryos, requires the greatest care. Human embryonic stem cells should be derived from two sources. The first are so-called "spare" embryos, those remaining after a couple has completed their family or for some other reason decided that they have no further use for their stored embryos. The second are embryos that are not of sufficient quality to be candidates for transfer to the uterus.

There are tremendous emotional, social, marital and financial strains associated with infertility. A couple grappling with infertility has very difficult decisions to make. Therefore it is necessary to adhere to the highest standards of protection for persons who are considering donation of their excess embryos for research purposes, with special concern for the informed consent and voluntariness of their decision.

Persons create embryos through in vitro fertilization with the intent of transferring one or more of them to the uterus, the hoped for outcome being a successful pregnancy and a healthy baby. Because the process of procuring eggs for IVF presents some risks to a woman's health, many women attempt to produce as many eggs from one cycle as possible. Because eggs cannot be frozen but embryos can, persons using IVF usually aim to produce a group of stored, frozen embryos to support as many attempts at pregnancy as necessary to achieve their goals. Often, they end up with more embryos than they need to use. Persons with excess embryos have the option of donating them to other infertile couples, destroying them, or donating them for research purposes.

[27] Public Health Service Act (42 U.S.C. 289) Section 498A.

Informed consent requires that the woman or couple, with substantial understanding and without inappropriate influences, authorize the use of their spare embryos for research. Because assisted reproduction is such a stressful and usually drawn-out process, informed consent should be secured in two stages. Like the model of organ procurement protocols, the consent process should also maintain a separation between personnel working with the woman or couple desiring to get pregnant and personnel requesting embryos for stem cell research.

At the beginning of the process, personnel working with the persons who hope to become pregnant should find out their preferences about what they want done with any possible spare embryos left over from the assisted reproduction process. Once a couple has definitely decided that it has completed its family, or for some other reason has no more use for the remaining embryos, then they should be approached a second time to secure an explicit consent to use the embryos in stem cell research.

Consonant with existing norms of good research practice, policies for securing embryos should include at least the following points:

(1) Women should not undergo extra cycles of ovulation and retrieval in order to produce more "spare" embryos in the hope that some of them might eventually be donated for research;

(2) Analogous with our current practice for organ donation, there should be a solid "wall" between personnel working with the woman or couple who hope to become pregnant, and personnel requesting embryos for stem cell purpose;

(3) Women and men, as individuals or as couples, should not be paid to produce embryos, nor should they receive reduced fees for their infertility procedures for doing so;

(4) All reasonable efforts should be made to obtain the consent of both gamete donors.

If these norms are adhered to, the procurement of embryos for the derivation of stem cells does not raise ethical problems which constitute a bar to research.

In addition, in order to allow persons who hold diverse moral positions on the status of the early embryo to participate in stem cell research to the greatest degree possible, stem cells (and stem cell "lines") should be identified with respect to their provenance. Patients and researchers should be able to avoid participating in stem cell use if the cells were derived in a way that they would consider to be unethical. As a matter of good scientific practice, records are routinely maintained on the sources of biological materials. It is of utmost importance that documentation of the original source of the stem cells can be made readily available to researchers and to potential recipients of stem cell therapies.

There are constraints with respect to the implementation of these policies. Fertility clinics, the primary source for embryonic stem cells, operate with virtually no federal oversight. It is important that policies and procedures be in place and that personnel be adequately trained so that donors are treated in an ethical manner. If the private sector fails to adopt appropriate measures, then the states or the federal government should consider establishing guidelines.[28]

[28] One model for this would be the recently established program to certify laboratories that provide assisted reproduction services. This program, initiated by the federal government, but up to the states to adopt, would create standards for, among other things, the quality of laboratory procedures, services, and personnel. Department of Health and Human Services, Centers for Disease Control and Prevention, "Implementation of the Fertility Clinic Success Rate and Certification Act of 1992—A Model Program for the Certification of Embryo Laboratories." *Federal Register 64*: 39374-39392 (21 July 1999).

Justice Considerations

The therapeutic potential of stem cells for treating and possibly curing many serious diseases constitutes a major rationale for large-scale investments of public and private resources in human stem cell research. To justify doing so, however, requires some assurance that people in need will have access to the therapies as they become available. Principles of justice are based on treating persons with fairness and equity and distributing the benefits and burdens of health care as fairly as possible in society. This would require equitable access to the benefits of stem cell research, without regard to the ability to pay.

Several factors make it unlikely, however, that there will be equitable access to the benefits of this research in this country. Unlike other western democracies, the United States does not have a commitment to universal health care. Currently the trends are in the opposite direction. 44.3 million people (16.3% of the United States population) lack health insurance and therefore do not have reliable access even to basic health care.[29] Others are underinsured. Moreover, if stem cell research results in highly technological and expensive therapies, health insurers may be reluctant to fund such treatments.

Another factor complicating the commitment to just access is the central role of the private sector in stem cell development. The private sector makes determinations about investments on the basis of potential profitability. This has several implications. The private sector will not invest resources in potential applications that they consider lacking in commercial value, but that may have considerable therapeutic promise. Commercial considerations will also affect the pricing of stem cell products. Here again, market concerns could raise prices, making stem cell therapies more expensive. Unless the federal government assumes a central role in setting priorities and investing in stem cell research, some of the most needed therapies may not be developed. These justice considerations are a further reason for encouraging federal support for stem cell research.

Problems of access and equity are even greater on a global level. Vastly unequal resources, differential standards of public health, and uneven opportunities for health care within and between countries comprise barriers to achieving even a semblance of distributive justice. The World Health Organization has reminded member states that "justice demands equitable access to genetic services." WHO has also stated that "Genetic services for the prevention, diagnosis and treatment of disease should be available to all, without regard to ability to pay, and should be provided first to those whose needs are greatest."[30] It will be difficult to achieve these norms in a global

[29] United States Census Bureau, *Health Insurance Coverage, 1998*. http://www.census.gov/hhes/www/hlthins.html.

[30] World Health Organization, "Proposed International Guidelines on Ethical Issues in Medical Genetics." Report of a WHO Meeting on Ethical Issues in Medical Genetics, Geneva, 15-16 December 1997. Available at: http://www.who.int/ncd/hgn/hgnethic.htm.

economy in which transnational corporations play a dominant role and disparities of all types are ever growing greater.[31]

Overcoming these hurdles and assuring equitable access to the benefits of stem cell research in this country will be a politically and financially challenging task. It is therefore appropriate to begin considering how to do so now in advance of the development of applications. Therefore, the federal government should consider ways to achieve equitable access to the benefits derived from stem cell research.

[31] Mathews, J.T., "Power Shift." *Foreign Affairs*, 76: 50-54 (1997); Slaughter, A.M., "The Real New World Order." *Foreign Affairs*, 76: 183-97 (1997).

Funding

Public and private research on human stem cells derived from all sources—embryonic, fetal, and adult—should be encouraged in order to support and contribute to the rapidly advancing and changing scientific understanding of the potential of human stem cells from these various sources. Embryonic stem cells (ES cells) derived from early embryos and embryonic germ cells (EG cells) have particular promise for a wide range of therapeutic applications because they are capable of giving rise to virtually any cell type. Research on these primordial cells will also provide a unique opportunity to study human cell biology. Adult stem cells, obtained from mature tissue, differentiate into a narrower range of cell types. As a result, many cells of medical interest cannot currently be obtained from adult-derived stem cells. It is also less feasible to develop large-scale cultures from adult stem cells. Nevertheless, because the study of human stem cells is at an early stage of development, it is difficult to predict outcomes and findings at this point in time. As more research takes place, the full developmental potential of different kinds of stem cells will become better understood.

To realize the potential health benefits of stem cell technology will require a large and sustained investment in research. The federal government is the only realistic source for such an infusion of funds. For those who are challenged daily by serious diseases that could in the future be relieved by therapies gained through stem cell research, public funding holds the greatest promise for sooner rather than later research results that can be transferred from the bench to the bedside. Without the stimulus of public funding, new treatments could be substantially delayed.

The commitment of federal funds also offers a basis for public review, approval, and monitoring through well established oversight mechanisms that will promote the public's interest in ensuring that stem cell research is conducted in a way that is both scientifically rigorous and ethically proper. Additionally, public funding can contribute to sound social policy by increasing the probability that the results of stem cell research will reflect broad social priorities that are unlikely to inform research in the private sector.

A substantial portion of the U.S. population, including many children, is excluded from the U.S. health care system. Public funding offers the best hope of fostering public consideration of the common good, rather than marketplace concerns, and of expanding access to the fruits of stem cell research for large numbers of Americans.

Historically, the availability of shared, canonical genetic stocks has been indispensable for the advancement of research in the life sciences. Stem cell research is more likely to advance if such canonical genetic stocks of ES cells are made available to the scientific community. Public funding under the auspices of federal agencies is the only effective means for ensuring equal access by scientists to standardized ES cell lines.

There are segments of American society that disagree on moral grounds with using public monies to support certain types of stem cell research. Faced with such disagreements, it

is important to recall that public policy in a pluralistic democracy cannot hope to incorporate all of the viewpoints and ethical priorities of the many ethical and religious perspectives that compose the body politic. The aim of public policy is more limited: to protect and promote the basic values essential to civic order and the pursuit of widely different individual conceptions of the good. An appreciation of these limits is not just a secular insight; it is deeply rooted in the religious traditions that have formed American culture, most of which recognize that not all their ethical beliefs, however important, require legal embodiment.

In the context of stem cell research, this understanding of the limits of public policy appears to lead to four practical conclusions. One is neutrality with regard to disputed questions of moral status and a permission for individuals, whether they are researchers or embryo or fetal tissue donors, to act in conformity to their own conscientious moral views on these matters. A second is the commitment to public involvement in research support when this research is reasonably related to the promotion and protection of public health. A third is respect for opposing views, especially those based on deeply held religious grounds, to the extent that this is consistent with the protection and promotion of public health and safety. A fourth is to make support available for research into alternative sources and/or methods for the derivation of stem cells and into further initiatives on adult stem cells.

Taken together, these four considerations do not appear to rule out public funding for research involving the use of stem cell lines derived from embryos and aborted fetuses. Support for this conclusion exists in the area of fetal tissue research, which has been funded by the National Institutes of Health since 1993. Although many Americans oppose abortion, the possible future health benefits of fetal tissue research, some of which are only now beginning to be substantiated, were widely taken as a reason for proceeding with public support of this research.[32] At the same time, strenuous efforts were made in crafting public policy and regulations governing this area to avoid or minimize public involvement in what some citizens regard as morally unacceptable decisions. The regulations designed to separate the abortion decision from the decision to donate tissue for research purposes, the disincentives to commercialization of fetal tissue, and the separation of funded researchers from involvement in the performance of abortions all reflect respect for the concerns and values of those opposing abortion.

Public funding should be provided for embryonic stem cell and embryonic germ cell research, but not at this time for activities involved in the isolation of embryonic stem cells. Although the derivation of stem cells can be carried out in an ethical manner, there is enough objection to the process of deriving stem cells to consider recommending against its public funding.

[32] The possible future benefits of fetal tissue research underlay the recommendations of the majority in the *Report of the Human Fetal Tissue Transplantation Research Panel* (1988).

Further, for the foreseeable future there will be sufficient material available for research isolated by researchers without using public funding.[33] This approach should provide adequate public funding for researchers to move expeditiously toward discoveries that will lead to alleviating the suffering caused by human disease.

[33] The Wisconsin Alumni Research Foundation (WARF) is the patent and license agent for the University of Wisconsin-Madison. WARF has assumed responsibility for patenting, licensing, and distribution of human embryo stem cells, which are the result of research by Dr. James Thomson. Although certain rights have been granted to Geron Corporation, WARF has retained rights involving the research use of human embryonic stem cells. WARF is currently working on a mechanism to support the supply of cells to academic and non-academic researchers that it expects to have finalized in October 1999. WARF intends to provide the cells to academic researchers for a nominal fee.

Oversight and Accountability

The appearance of new technology can evoke apprehension and engender uncertainty among segments of the population about its uses. Where these concerns are related to issues having important ethical and social implications, certain levels of oversight are appropriate. But it is important to create new oversight mechanisms or regulatory burdens only when there are compelling reasons for doing so. Public oversight should be in proportion to the seriousness of the concerns raised.

Although some adjustments in the current system of oversight are necessary, no new regulatory mechanisms are needed at the present time to ensure responsible social and professional control of such research in the United States. A system that has, over time, protected the public health and safety while simultaneously providing a setting that is congenial to the advancement of science has much to offer. The basic framework is sound and includes several attractive features:

- It is pluralistic, with multiple access points for those who wish to be heard and influence public policy.
- It is democratic, with public involvement encouraged on different levels and at different points in the drafting, consideration, and promulgation of public policy.
- It is flexible, in that it can adapt to accommodate cutting-edge research and innovative technology.
- It is compatible with the values of scientific freedom and public accountability.
- It supports private-public partnerships consistent with the distinct yet complementary goals of the private sector and government.

Despite these strengths of the existing framework for oversight of research, as the science advances, new issues may emerge that will challenge acceptable ethical practices and public policy. As human stem cell research proceeds, there should be opportunities for public reconsideration of the need for any special institutional oversight, and we strongly recommend an open, informed, and continuing public discourse on these matters.

Private Sector Oversight

Although public funds have been expended in support of adult stem cell research, to date all advances in human embryonic and fetal germ cell research have come from the private sector, underwritten by biotechnology companies in the hope that products will be developed for medical therapy. This raises important questions about whether ethical and broader social considerations can be adequately addressed by continued exclusive funding by the private sector. The addition of the public oversight that accompanies federal funding offers substantial advantages. Such advantages include increased research

productivity, earlier results from the research, a broader range of participation by academic scientists, increased public understanding and support, and greater possibilities that therapies will be developed with consideration for the public good will.

Private sector sponsorship of research certainly does not preclude a degree of oversight or adherence to ethical practices. Geron Corporation, the private company sponsor of all published human embryonic and germ cell research to date, convened an Ethics Advisory Board (EAB) in September 1998 to develop guidelines for the ethical conduct of stem cell research. The EAB sought further public discourse by inviting *The Hastings Center Report* to publish its findings complete with dissenting views.[34] If such boards were to become institutionalized by the private sector, they would have the most credibility and weight if they reviewed ethical and social issues during the start-up phase of research, had a multidisciplinary membership, including representatives from the local community, and gave minimum, if any, financial compensation for service. Their impact would be greatest if they shared their own findings and recommendations with other companies. However, even with the best of intentions, if a private company establishes its own EAB but disapproves of the Board's findings, there is no guarantee that the company would abide by the EAB's conclusions and recommendations. This could undermine public confidence and raise anxiety about the manner in which stem cell research is proceeding.

There are other concerns associated with sole reliance on private sector funding of stem cell research. There is the very real possibility that market forces and perceived investment opportunities by companies will, in the absence of federal funding, exert a disproportionately powerful influence on the development of stem cell research without adequate attention to public priorities. One result could be that the focus of such research will be on diseases likely to lead to profit at the expense of less common but more severe diseases. There is also the possibility that stem cells will become caught up in an expanded marketing of human body parts. In a day when the market for individual genes, or even gene fragments, holds lucrative possibilities,[35] great caution should be taken in ceding domain to this area of research to the private sector in the absence of open and widespread public consultation.

Intellectual Property Considerations

The appropriateness of patenting life forms has been a source of considerable controversy in this country. Until 1980, life forms were considered to be "products of nature" and ineligible for patent protection. In the twenty years since the first biotechnology patents were granted, various critics have claimed that the patenting of living things promotes a reductionist conception of life that removes any distinction between living and non-living things. Some scientists and lawyers have questioned whether these patents promote the

[34] Symposium. "Stem Cell Research." *The Hastings Center Report*, 29: 33-48 (March-April 1999).

[35] While just in its infancy, the potential market for gene-specific pharmaceuticals is huge. For the biotechnology industry's view of this topic, see: http://www.forbes.com/specialsections/biotech99/01.htm.
For a specific example of a patent held on a partial gene sequence for potentially very important diagnostics and drugs, see: http://www.incyte.com/news/1998/PR9829-estpatent.html.

advancement of science. Several ethicists have argued that genes and genetically modified organisms should be considered part of the common heritage of all people. Other thinkers and advocates have raised equity issues about the role of patents in impeding development and access to beneficial technologies.[36]

In response, the biotechnology industry has emphasized the need for patent protection to warrant the very large investments and long time periods usually required for the development of biotechnology. Proponents of life patents typically emphasize that the products being patented do not occur in nature, but are isolated and purified forms representing important technological advances. It is also claimed that strong biotechnological patent protection in the U.S. has been a major factor facilitating U.S. leadership in this field.[37]

The U.S. Patent and Trademark Office (PTO) has already stated that purified and isolated stem cells are patentable subject matter.[38] According to the PTO, stem cell products and research tools meet the three criteria for patentability: novelty, utility, and nonobviousness.[39]

When research is funded entirely by the private sector, as is currently the case with stem cell research, it is a private matter whether, and under what terms, new intellectual property is obtainable for commercial or research purposes. Corporations can, for example, make the stem cell products over which they hold patents available only under a very restrictive material transfer agreement. They can also set the terms, including limitations that reduce access to these cells.

Given the promise of stem cell research, it is important to encourage the development of broadly beneficial therapeutic products with widespread access. Government investment in promising areas of research would enable federal agencies and laboratories to hold patents and to exercise them in ways that enhance development and dissemination of stem cell technology. To maximize this public benefit, Congress or the PTO could take steps to ensure that research tools are obtained in ways that protect basic and future

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[36] For a discussion of some of these issues see Chapman, A.R., ed., *Perspectives on Genetic Patenting: Religion, Science and Industry in Dialogue* (Washington, D.C.: American Association for the Advancement of Science, 1999).

[37] Nossinghoff, G.J., and Bombelles, T., "The Importance of Intellectual Property Protection to American Research. Intensive Pharmaceutical Industry.**"** *The Columbia Journal of World Business***,** Spring: 38-47 (1996).

[38] Todd Dickinson, Acting Assistant Secretary of Commerce and Acting Commissioner of Patents and Trademarks, so informed the Subcommittee on Labor, Health and Human Services, Education and Related Agencies of the Senate Appropriations Committee on 12 January 1999; see http://www.senate.gov/~appropriations/labor/Dickins.htm.

[39] As interpreted by the Patent and Trademark Office (PTO), to be "novel" an invention must not have been known and available to the public at the time of the application. "Utility" refers to usefulness. To qualify, a proposed patent must specify a concrete function, service, or purpose. According to the criteria of "non-obviousness" an invention cannot obtain a patent if the differences between its specific subject matter and the prior art are such that "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (35 United States Code, Sec. 103).

product development. One way of doing this is to define a strong research exemption that would give third parties access to stem cell products and research tools for research purposes without having to obtain permission from the patent holder. Another would be to negotiate non-exclusive licenses whenever possible. Still another possibility is to require compulsory licensing under limited and clearly defined circumstances.

Public Sector Oversight

While efforts by the private sector to provide for ethical review of controversial research are to be applauded, for all of the above reasons a clear federal role in funding and oversight would be far superior to a research endeavor left solely to private institutions. The use of federal funds to support all forms of stem cell research will assure that, where needed, proper oversight mechanisms and guidelines will evolve in order to promote the advancement of promising medical research, balanced with a healthy respect for the American public's expectations for research conducted according to the highest ethical standards.

Federal funding would automatically trigger a set of oversight mechanisms now in place to ensure that the conduct of biomedical research is consistent with broad social values and legal requirements. While basic laboratory research with personally non-identifiable stem cells does not pose any special ethical or oversight challenges, an elaborate system of review is in place for research involving human subjects. The Federal Common Rule[40] governing human subjects research provides for local and federal agency review of research proposals in such circumstances, weighing risks against benefits and requiring informed and voluntary consent. The Food and Drug Administration (FDA) has the authority under the Public Health Service Act and the Food, Drug, and Cosmetic Act to regulate the development and use of human stem cells that will be used as biological products, drugs, or medical devices to diagnose, treat, or cure a disease or underlying condition.[41] Additionally, the FDA has proposed developing product standards for hematopoietic stem/progenitor cell products intended for allogenic use in recipients unrelated to the donor.[42] This proposal is intended to "streamline regulatory requirements…while providing adequate protection to the public health,"[43] where cellular products posing increased risk to health or safety would be required to undergo clinical trials as investigational drugs, biologics, or devices, and to secure FDA approval prior to marketing. This approach, which relies on existing regulatory authority, is consistent with the one recommended in this report. The federal government's *Model Program for the Certification of Embryo Laboratories* should be generally endorsed and its adoption by the states strongly encouraged. The program is a useful first step toward achieving

[40] Title 45, Code of Federal Regulations, Section 46.
[41] Brady, R.P., Newberry, M.S., and Gerard, V.W., "FDA Regulatory Controls Over Human Stem Cells." *Professional Ethics Report XII*: 5-6 (1999).
[42] Department of Health and Human Services, Food and Drug Administration., "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placenta/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products: Request for Comments." *Federal Register 63*: 2985-2988 (1998).
[43] *Ibid.*, p. 2985.

greater quality control in private fertility clinics that obtain, store, and implant human embryos.

Complementing these regulatory mechanisms are two national advisory bodies. The National Bioethics Advisory Commission (NBAC), which has issued its own recommendations for stem cell research,[44] has demonstrated its legitimate claim to respect for its efforts as a national body to promote public input into social policy related to advances in biomedical research. The Recombinant DNA Advisory Committee (RAC) currently has a mandate to review ethical and policy issues associated with human gene therapy and could be authorized to change its mission to broaden its purview. Almost two decades of experience with RAC suggest that it could be an effective institutional focal point within the federal government to facilitate the type of public dialogue on stem cell research proposed here, and to coordinate efforts to develop new guidelines, where needed. The RAC has a proven track record of providing an open forum for sorting out complex ethical issues and of defusing conflict. Furthermore, it has acquired a degree of legitimacy among scientists in both the public and private sectors, with its *Points to Consider*[45] in the design and conduct of gene therapy research widely accepted. This experience of functioning as a sort of national research ethics committee for gene therapy research protocols from 1984-1994,[46] indicates that federal oversight can be effective in fostering rigorous scientific and ethical review and in encouraging public participation in the process.

These federal bodies should work with interested stakeholders in the conduct of stem cell research—professional organizations, patient disease groups, religious communities, the Congress, funding agencies and private foundations, industry, and others—so that the public can be assured that appropriate safeguards are in place as this research evolves. Furthermore, there are some ethical and policy issues that, while not unique to stem cell research (e.g., intellectual property claims, creation of new life forms, commercial sale of tissue), should be part of any broader discussion among those stakeholders.

There are advantages to using this approach. The most obvious one is that it avoids the need to create a new administrative and costly structure when existing mechanisms are in place that could be readily adapted to achieve the objectives of oversight without impeding promising research. This approach balances the promise of scientific innovation with serious consideration of public concerns about a novel technology that manipulates human tissue. It encourages public involvement in national discussions and in deliberations on policy. It permits flexibility through incremental adjustments in guidelines and/or policy in anticipation of or in response to changes in knowledge or technology. It also relies on a system with which researchers in both the private and public sectors and

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[44] The executive summary is available online: http://bioethics.gov/stemcell_exec_intro.htm. For information about the full report, see: http://bioethics.gov/pubs.html.

[45] Sometimes referred to as "Appendix M," the "Points to Consider" is found in the document *Guidelines for Research Involving Recombinant DNA Molecules* (last update May 1999). See: http://www.nih.gov/od/orda/toc.htm (Guidelines), http://www.nih.gov/od/orda/apndxm.htm (Appendix M).

[46] For an overview of the history of gene therapy, including the role of RAC, see Coutts, M.C., "Human Gene Therapy." *Scope Note 24* (1994). National Reference Center for Bioethics Literature, Georgetown University. Available online at http://www.georgetown.edu/research/nrcbl/scopenotes/sn24.htm.

their institutions are accustomed. Therefore, both the ethical and legal requirements governing research will be familiar to them as they plan and conduct their studies. And it acknowledges the scientific contributions made by the private sector and supports public-private partnerships by encouraging the private sector to contribute to the development of ethical guidelines and professional standards for the conduct of stem cell research.

Conclusion

The pursuit and production of knowledge through scientific research is an undertaking that offers enormous intellectual rewards for researchers while also performing an important social function. The advancement of science has transformed our lives in ways that would have been unpredictable just a half-century ago. Whether stem cell research will have a similar effect remains to be determined, but the promise is so great that it seems wise to consider seriously how best to further such research in a manner that is sensitive to public sensibilities. Public conversations about research and use of human stem cells are well underway. This report is intended to contribute to and inform this ongoing dialogue.

We recognize that science does not exist in isolation from the larger community that feels its effects, whether perceived as good or bad. The work of scientists is, and should be, conditioned and directed by consideration of broader human values. This means that the development of public policy, especially where highly controversial matters are involved, must take all interested sectors of the public into account. It is only through broad-based participation that the values of all stakeholders in the research enterprise can be carefully considered and weighed. We hope that this report has offered an approach that balances the promise of human stem cell research with the public's genuine concerns about such research in a manner that will lead to a consensus on how best to proceed.

Glossary

Adult stem cell. Any stem cell taken from mature tissue, regardless of the age of the donor.

Autologous transplant. Transplant using tissue from the same individual, or a twin.

Allogeneic transplant. Transplant using tissue from a donor individual not genetically identical to the recipient.

Autoimmune diseases. A constellation of different diseases all characterized by the failure of the body to distinguish "self" from "non-self" causing the body to attack its own tissues.

Blastocyst. A preimplantation embryo of 30-150 cells.

Cell lines. Cultures of disaggregated tissue that can be maintained and propagated for use in research. The length of time cells will survive in culture varies. Some cell lines are *immortalized*; that is, they can be maintained essentially indefinitely, for one of a variety of reasons. Embryonic stem cells and embryonic germ cells are immortal because they express telomerase, one of the factors necessary for cells to propagate normally.

Chimera. An individual, organ, or part of an organism consisting of tissues of diverse genetic constitution.

Clinical trial. Research to test the safety and efficacy of new treatments or to compare the effects of different treatments in patients or healthy volunteers.

Cryopreservation. The process of freezing biological materials in such a way that they can be stored for long periods of time, then thawed for use.

Ectoderm. The outermost of the three primary layers of an embryo; produces the nervous system, the epidermis and epidermal derivatives, and the lining of various body cavities such as the mouth.

Ectopic tissue. Tissue that has formed abnormally temporally or spatially.

EG cells. Embryonic germ cells. These cells are found in a specific part of the embryo/fetus called the gonadal ridge, and normally develop into mature gametes.

Embryo. Organisms in the early stages of growth and development. In animals, embryos are characterized by the cleavage of the fertilized eggs to many cells, the laying down of the three germ layers, and formative steps in organ development. Although there is some discussion about the characteristics marking the switch from embryo to fetus, in human beings, "embryo" generally refers to the time from implantation to about eight to twelve weeks after conception.

Endoderm. One of the three primary layers of an embryo; it is the source of the digestive tract and other internal organs.

ES cells. Embryonic stem cells.

Eukaryotic. Organisms composed of cells that have a nucleus (*i.e.*, the nucleus, where the genetic material resides, is separated from the rest of the cell, called the cytoplasm, by a complex membrane called the nuclear envelope).

Fetus. Organisms in later stages of development. In human beings, approximately eight to twelve weeks after conception.

Gamete. General term describing sperm and eggs.

Gene therapy. The use of genetic material, usually DNA, to correct inherited or accumulated genetic damage.

Genome. The complete genetic code for any individual or species.

Germ cells. Cells comprising actual reproductive components of an organism (specifically, eggs and sperm, and their precursors).

Hematopoietic stem cell. Refers to a particular kind of stem cell that can restore blood.

Immortalized cell line. See *Cell lines.*

Informed consent. Autonomous authorization of a medical invention or involvement in research based on substantial understanding.

In vitro. Refers to processes taking place in test tubes or similar containers.

In vivo. Refers to processes taking place in an organism.

Mesoderm. One of the three primary layers of an embryo; produces muscle, bone, and other related tissues.

Mesenchymal stem cell. A particular kind of stem cell that may give rise to tissues of mesodermal origin, including muscle, bone, and related tissues.

Monoclonal antibodies. Antibodies produced in the laboratory by specialized cells called hybridomas. The important features of these antibodies include their specificity of binding to a single antigen (protein), the ability to produce them in unlimited amounts, and their homogeneity. These antibodies have proven to be very useful in the detection of several diseases (including, but not limited to, cancer and various viral infections) and in therapy (for certain cancers).

Pluripotent. Referring to cells able to give rise to virtually any tissue type, but not to a functioning organism.

Primordial germline cells. The source of embryonic germ cells. In normal development, these are the cells that give rise to eggs or sperm.

Recombinant DNA. Molecules that are constructed outside living cells by joining natural or synthetic DNA segments in such a way that they can replicate in a living cell (the replicative products are also considered to be recombinant DNA).

Somatic cells. Refers to cells of the body excluding germ (reproductive) cells.

Stem cell. In general, a cell with the capacity to reproduce itself, and to produce distinct differentiated tissue.

Trophoblast. The outer layer of cells of the mammalian blastocyst that gives rise to the placenta.

Totipotent. Refers to cells able to give rise to virtually any tissue type and, in some cases, as shown experimentally in mice, to a functioning organism.

Appendix I

Working Group Members

Andrea L. Bonnicksen, Ph.D., is professor and former chair of the Department of Political Science at Northern Illinois University, where she teaches courses in biomedical and biotechnology policy. She publishes on issues related to reproductive and genetic technologies. Dr. Bonnicksen is a member of the Ethics Committee of the American Society for Reproductive Medicine.

David M. Byers, Ph.D., is executive director of the Committee on Science and Human Values, National Conference of Catholic Bishops. The Committee conducts dialogues with scientists on a wide variety of issues, bringing Catholic theology and moral thought into contact with advances in modern science and technology.

Courtney Campbell, Ph.D., is associate professor of Philosophy at Oregon State University, and the director of the Program for Ethics, Science, and the Environment. He has written extensively on biomedical ethics, including papers for the National Bioethics Advisory Commission on human cloning and on research on human tissue. Dr. Campbell had previously been a research associate at The Hastings Center and was the editor of *The Hastings Center Report*.

Dena S. Davis, J.D., Ph.D. (Religious Studies), is associate professor at Cleveland-Marshall College of Law. She writes frequently on issues of genetics and reproduction. In 1998-1999, she was a Visiting Scholar at the National Human Genome Research Institute (NIH). She is legal consultant to the Committee on Bioethics of the American Academy of Pediatrics.

Abigail Rian Evans, M.Div, Ph.D., is Charlotte W. Newcombe professor of practical theology, and academic coordinator of field education at Princeton Theological Seminary. She specializes in bioethics and health ministries, and is especially concerned with recapturing the historic health and healing ministry of the early church. Her books *Redeeming Marketplace Medicine* and *The Healing Church* address a theologically based health care reform model, a subject she was involved in while serving on the Clinton Health Care Task Force. Since the 1980s she has done research and writing on genetics, especially concerning reproductive technologies. Dr. Evans is an ordained minister in the Presbyterian Church (USA).

Kevin T. FitzGerald, S.J., Ph.D., is a Research Associate in the Department of Medicine and the Medical Humanities Program at the Loyola University Medical Center in Chicago. His two principal research foci are the investigation of abnormal gene regulation in cancer and ethical issues in medical genetics. He is currently completing a second doctorate in bioethics. Father FitzGerald is a Roman Catholic priest and a member of the Society of Jesus (Jesuits).

Norman Fost, M.D., M.P.H., is Professor of Pediatrics and Director of the Program in Medical Ethics at the University of Wisconsin School of Medicine. There, he is chair of the Health Sciences Human Subjects Committee, the Institutional Review Board responsible for the stem cell research conducted by James Thomson. He also chairs the University's Bioethics Advisory Committee. Dr. Fost is past chair of the American Academy of Pediatrics Committee on Bioethics and was a member of the Clinton Health Care Task Force.

Robert Goldman, Ph.D., is the Stephen Walter Ranson Professor and Chairman of the Department of Cell and Molecular Biology, Northwestern University School of Medicine. His laboratory's research focuses on the structure and function of intermediate filaments of cellular cytoskeletal systems that shape cells and allow them to carry out diverse physiological functions. Dr. Goldman is a Fellow of the American Association for the Advancement of Science and a member of its Board of Directors. He has taught at the Woods Hole Marine Biological Laboratory and is Co-Director of the Science Writing Fellowship Program there.

Robert A. Goldstein, Ph.D., M.D., currently serves as the Vice President for Research of the Juvenile Diabetes Foundation (JDF), and is responsible for planning and administration of their research funding programs aimed at finding a cure for Type 1 Diabetes and its complications (in FY2000, JDF will fund more than $75 million in grants and training awards). Prior to joining JDF in 1997, he was Director, Division of Allergy, Immunology and Transplantation at the National Institute of Allergy and Infectious Diseases (NIH).

David Gottlieb, Ph.D., is Professor of Neurobiology at Washington University School of Medicine in St. Louis, Missouri. About 5 years ago his research interests in brain development lead him to study ES cells as a potential model system. Together with colleagues at Washington University, he demonstrated that ES cells could be efficiently differentiated into neurons and glia. He is currently utilizing this system to explore mechanisms of neural differentiation and is part of a team investigating their application to spinal cord injury research.

Ronald M. Green, Ph.D., is the Eunice and Julian Cohen Professor for the Study of Ethics and Human Values in the Religion Department, Dartmouth College, and is the Director of Dartmouth's Ethics Institute. In 1994, he was a member of the National Institutes of Health Human Embryo Research Panel. In 1996-97, he served, half time, as the founding director of the Office of Genome Ethics at NIH's National Human Genome Research Institute. Dr. Green has been president of the Society of Christian Ethics and is Secretary of the American Academy of Religion, the largest association of scholars of religion in the United States.

Daniel R. Marshak, Ph.D., is Senior Vice President and Chief Scientific Officer of Osiris Therapeutics Inc., a biotechnology company in Baltimore, Maryland, specializing in adult stem cell products for Regenerative Medicine. He holds an appointment as Adjunct Associate Professor of Oncology and of Molecular Biology and Genetics at The

Johns Hopkins University School of Medicine. Dr. Marshak currently serves on the Editorial Board of *The Journal of Biological Chemistry* and the Scientific Advisory Board of the Dystonia Medical Research Foundation.

C. Ben Mitchell, Ph.D., is consultant on biomedical and life issues for the Southern Baptist Ethics and Religions Liberty Commission, the moral concerns, public policy, and religious liberty agency of the Southern Baptist Convention. He teaches bioethics and contemporary culture at Trinity International University in Deerfield, Illinois. He has written widely in the area of bioethics and public policy, served on the AAAS working group on gene patenting, and is editor of the *American Journal of Ethics & Medicine*.

Daniel Perry is Executive Director of the not-for-profit Alliance for Aging Research in Washington, D.C. His organization promotes a broad agenda of medical and behavioral research for improving the health and independence of older Americans. He also chairs the Patients' Coalition for Urgent Research (Patients' CURe), an umbrella group of more than 30 national patient advocacy groups that works to project the concerns of patients and their families into public deliberations over stem cell research.

Robert Wachbroit, Ph.D., is a Research Scholar at the School of Public Affairs' Institute for Philosophy and Public Policy at the University of Maryland. He is also Adjunct Associate Professor of Obstetrics and Gynecology in the University's School of Medicine as well as a Senior Research Fellow at the Kennedy Institute of Ethics at Georgetown University. From 1987 to 1991, he held a joint appointment with the Institute for Philosophy and Public Policy and the Maryland Biotechnology Institute's Center for Public Issues in Biotechnology.

Gillian R. Woollett, M.A., D.Phil., is Associate Vice President for Biologics and Biotechnology at the Pharmaceutical Research and Manufacturers of America (PhRMA). In addition to overseeing all activities concerning biologics and biotechnology, her responsibilities include staffing the PhRMA Biomedical Research Key Issue Team (a high level industry forum for the discussion of the promise, ethics, and impact of new DNA technologies in health care, among other topics). Dr. Woollett also has responsibility for representing the pharmaceutical industry internationally, for example, by contributing industry ideas to the development of the proposed Compliance Protocol to be added to the Biological Weapons Convention.

Advisor

Laurie Zoloth, Ph.D., is Associate Professor of Social Ethics and Jewish Philosophy and Chair of the Jewish Studies Program in the College of Humanities at San Francisco State University. She is on the national board of the American Society for Bioethics and Humanities and is a member of the advisory committee for the Program of Dialogue on Science, Ethics, and Religion (AAAS). Dr. Zoloth is also a member of the Geron Ethics Advisory Board. Her most recent book is *Health Care and the Ethics of Encounter: A Jewish Discussion of Social Justice*, and she is co-editor with Dena S. Davis of *Notes from a Narrow Ridge: Religion and Bioethics*.

Appendix II

Staff

American Association for the Advancement of Science

Audrey R. Chapman, M.Div., Ph.D., who serves as director of two AAAS programs, the Dialogue on Science, Religion, and Ethics and Science and Human Rights, is trained both as a social scientist and religious ethicist. She is the author or editor of 14 books, including the just published *Unprecedented Choices: Religious Ethics at the Frontiers of Genetic Science*. She is one of the authors of the AAAS/ICS Stem Cell report.

Mark S. Frankel, Ph.D., is director of the AAAS Scientific Freedom, Responsibility and Law Program, where he develops and manages the Association's science, ethics and law activities. He is editor of *Professional Ethics Report*, a AAAS Fellow, and has published extensively on the ethical and legal implications of advances in biomedicine. He is one of the authors of the AAAS/ICS Stem Cell report.

Michele S. Garfinkel, Ph.D., is a Program Assistant in the AAAS Scientific Freedom, Responsibility and Law Program. Prior to joining AAAS, she was a post-doctoral Fellow at the Fred Hutchinson Cancer Research Center in Seattle. She is one of the authors of the AAAS/ICS Stem Cell Report.

Institute for Civil Society

Gail Pressberg, a Senior Fellow at the Institute for Civil Society, has been a social change activist for 25 years. Prior to her assignment at ICS, she was Director of the Center for Israeli Peace and Security of Americans for Peace Now; Executive Director of the Foundation for Middle East Peace; and a Staff Director at the American Friends Service Committee.

Appendix III: About AAAS and ICS

American Association for the Advancement of Science

Founded in 1848, AAAS is the world's largest federation of scientific and engineering societies with nearly 300 affiliates. In addition, AAAS counts more than 140,000 scientists, engineers, science educators, policy makers and interested citizens among its individual members, making it the largest general science organization in the world. The objectives of AAAS are to further the work of scientists, to facilitate cooperation among them, to foster scientific freedom and responsibility, to improve the effectiveness of science in the promotion of human welfare, to advance education in science, and to increase public understanding and appreciation of the methods of science in human progress.

The AAAS Directorate for Science and Policy Programs is home to the two Programs organizing this project on stem cell research and applications. The Scientific Freedom, Responsibility and Law Program is charged by AAAS with lead responsibility for the Association's activities related to ethics and law. It has organized a series of studies and public events related to advances in biomedicine, resulting in several publications: *The Genome, Ethics and the Law Issues in Genetic Testing* (1992*); Ethical and Legal Issues in Pedigree Research* (1993); *The Genetic Frontier: Ethics, Law, and Policy* (1994); and *Exploring Public Policy Issues in Genetics* (1997). In May-June 1996, the Program sponsored a series of four briefings on the social policy implications of the Human Genome Project for Members of Congress and their staffs.

The other program organizing this project is the AAAS Program of Dialogue on Science, Ethics, and Religion. Established in 1995, it has three objectives: (1) to promote knowledge about developments in science and technology within the religious community; (2) to provide opportunities for dialogue between members of the scientific, secular ethics, and religious communities; and (3) to promote collaboration between members of the scientific and religious communities on projects that explore the ethical and religious implications of scientific developments. The Program convened an eighteen-month dialogue on human gene patenting, involving the scientific, biotechnology, religious, and legal communities, resulting in the publication of *Perspectives on Gene Patenting: Science, Religion, and Industry in Dialogue*.

The two Programs co-sponsored a forum on human cloning in June 1997 and convened a second forum in September 1997 on human germline interventions.

Institute for Civil Society

Inspired by Eastern European movements that overthrew communism by the sheer force of belief in freedom, the Institute for Civil society (ICS) holds that joint action by people

in communities is as important as the actions of government and business in upholding democracy.

Established in 1995, and based in Newton, Massachusetts, ICS focused initially on forging relationships with grassroots groups to reduce handgun violence and improve the quality of life in Boston. In 1996, it received an endowment of $35 million that enabled it to expand its reach, and launched a national New Century/New Solutions project to renew civil society and highlight community perspectives in other parts of the country. ICS currently works in four program areas. *Democratic Capitalism* seeks to bridge the gap between those who have access to the capital that can make things happen, and those who do not. *Health and Science Policy* contributes to new ways of thinking about complicated issues, such as the relationship between biotechnology and cures for disease. *Culture and Creativity* identifies ways in which institutions, such as schools, can help to foster innovative thinking. *Violence* works to change the conditions that make violence possible.