

REPORT 5 OF THE COUNCIL ON SCIENTIFIC AFFAIRS (A-03)
Cloning and Stem Cell Research
(Reference Committee E)

EXECUTIVE SUMMARY

Objectives. – To provide an update on the scientific advances in stem cell research since 1999 and present recommendations.

Data Sources. – Literature searches were conducted in the MEDLINE database for English-language articles published between 1998 and April 2003 using the search terms “stem cells” in conjunction with “human” and “cloning.” The Council on Scientific Affairs (CSA) report, “Cloning and Embryo Research” (CSA Report 7, A-99), was used to identify references prior to 1999. The World Wide Web was searched for articles relating to stem cell research. Scientists from biotechnology companies involved in adult (Osiris Therapeutics, Baltimore MD) and embryonic (Geron Corporation, Menlo Park, CA) stem cell research were also consulted to gain an industry perspective on this technology.

Results. – Stem cells hold tremendous promise for treating a wide variety of human diseases as well as answering some basic biological questions regarding development. There are 2 sources of human embryonic stem cells: embryonic stem (ES) cells isolated from the pre-implantation embryo (blastula) and embryonic germ cells isolated from the genital ridge of the post-implantation embryo (fetus). Animal models provide strong evidence that stem cells can be successfully transplanted into target tissue and functionally integrated into existing systems, supporting the potential of these cells for regenerative therapy. Somatic cell nuclear transfer (SCNT) enables the generation of stem cells that are specifically tailored for an individual. The technique involves removing the nuclear material from a donor oocyte (enucleation) and replacing it with the nucleus from a somatic cell (nuclear transfer). SCNT technology is also being utilized in more basic research applications to understand molecular and cellular events underlying human diseases. However, recent legislation restricting the use of human embryos in research has limited access of U.S. laboratories to human ES cells. Generation of additional human ES cell lines via technology such as SCNT is still possible in laboratories not using federal funding but pending legislation would criminalize this type of research as well as prevent importation of cell lines developed outside this country. There is fear that much of the work conducted on human stem cells will shift to other countries if federal legislation is approved banning the generation of new ES cells in the United States. Recent studies have demonstrated that stem cells also exist in many types of adult tissue. One of the main questions surrounding adult stem cells is whether they are truly pluripotent like their embryonic counterparts or have a more limited potential (multipotent). While adult stem cell plasticity remains controversial, their possible use in repairing diseased tissue remains promising. It is anticipated that human stem cells will one day play a major role in preventing and alleviating human disease. The question of whether adult or ES will have a greater impact in regenerative medicine remains to be answered.

Conclusions. – Advances in stem cell research continue at a rapid pace. These developments continue to support the potential use of human stem cells in clinical applications, although significant hurdles remain before they will be in widespread use. Thus, the use of multipotent stem cells in biomedical research, including adult and cord blood stem cells, should be supported. The use of SCNT technology for regenerative medicine (therapeutic cloning) should also be supported while the use of this technology for the specific purpose of producing a human child (reproductive cloning) should not. However, ethical considerations should be acknowledged and evaluated as research in SCNT technology proceeds. Federal funding to support research involving human pluripotent stem cells should be encouraged. Previous conflicting AMA policies (H-460.917, H-460.925, and H-460.937 [AMA Policy Database]) should be rescinded in favor of a new policy reflecting the above views.

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

CSA Report 5-A-03

Subject: Cloning and Stem Cell Research
(Resolution 511, A-02)

Presented by: Scott D. Deitchman, MD, MPH, Chair

Referred to: Reference Committee E
(D. Robert McCaffre, MD, Chair)

1 Background

2
3 American Medical Association (AMA) policy on stem cells, the use of somatic cell nuclear transfer
4 technology (SCNT), and cloning has evolved over the last decade in response to scientific and technical
5 advances. Although current policy provides useful guidance on some issues, it is conflicted on others (see
6 below).

7
8 Additionally, Resolution 511, introduced by the Texas Delegation and referred to the Board of Trustees at
9 the 2002 Annual Meeting, asked:

10
11 That our AMA ask the Council on Scientific Affairs (CSA) to develop a report on the likelihood
12 of adult sources of stem cells being practical in the foreseeable future.

13
14 Therefore, the CSA agreed to provide an update on scientific advances in stem cell research and, in
15 conjunction with a companion report offered by the Council on Ethical and Judicial Affairs, clarify AMA
16 policy in this area. A Glossary of Terms used in this update is provided at the end of this report.

17
18 Introduction

19
20 Stem cells are a unique population of unspecialized cells characterized by their ability to continuously
21 renew themselves for long periods of time through cell division. While stem cells have been isolated from
22 both embryonic and adult tissues, they differ in several properties including the ability to differentiate into
23 specialized cell lineages. Much of the initial biology of stem cells was based on isolates from murine
24 embryos. The ability to isolate human embryonic stem (ES) cells has rekindled expectations that these
25 cells will play a major role in regenerative medicine but at the same time has raised new concerns about
26 the use of human embryos in biomedical research.

27
28 Human ES cells are commonly derived from unused fertilized eggs (supernumerary embryos) donated by
29 in vitro fertilization clinics with informed consent of the donor. Alternatively, stem cells have also been
30 obtained from embryos generated from unfertilized eggs using a technique called somatic cell nuclear
31 transfer (SCNT). Initially, SCNT technology was designed to produce embryos from which
32 immunologically compatible stem cells could be derived for use in treating human diseases (therapeutic
33 cloning). However, recent advances in the technology have prompted concerns about embryos formed by
34 SCNT being misused for generating human clones (reproductive cloning).

1 Methods

2
3 Literature searches were conducted in the MEDLINE database for English-language articles published
4 between 1998 and April 2003 using the search terms “stem cells” in conjunction with “human” and
5 “cloning.” The CSA report, “Cloning and Embryo Research” (CSA Report 7, A-99), was used to identify
6 references prior to 1999. The World Wide Web was searched for articles relating to stem cell research.
7 Scientists from biotechnology companies involved in adult (Osiris Therapeutics, Baltimore MD) and
8 embryonic (Geron Corporation, Menlo Park, CA) stem cell research were also consulted to gain an
9 industry perspective on this technology.

10 11 Summary of Current AMA Policy on Stem Cells, Cloning, and SCNT

12
13 Relevant policies and ethical opinions (AMA Policy Database) are:

- 14 • E-2.147 Human Cloning (I-99)
- 15 • H-460.917 Science, Policy Implications, and Current AMA Positions Regarding
- 16 Embryonic/Pluripotent Stem Cell Research and Funding (CSA Rep 15, I-99)
- 17 • H-460.937 Cloning and Human Embryo Research (BOT Rep. 13, A-95; CSA Rep.7, A-99)
- 18 • H-140.930 The Ethics of Human Cloning (CEJA-2, A-99)
- 19 • H-460.925 Scientific Implications of Somatic Cell Transfer Technology (Res 11, A-98)

20
21
22 See the Appendix for the complete text and comments on these policies.

23
24 AMA policy opposes the cloning of human beings at this time, and the use of SCNT technology for
25 reproductive cloning. AMA policy also strongly endorses federal funding for research involving human
26 ES cells (Policy H-460.917). Specific elements are based on support of the 1999 National Bioethics
27 Advisory Commission (NBAC) report, *Ethical Issues in Human Stem Cell Research*. This report
28 recommended federal support for stem cell research involving fetal cadavers, or embryos remaining after
29 infertility treatments, but opposed creation of embryos (by in vitro fertilization or SCNT) solely for the
30 purpose of research on human ES cells. This latter view is in contrast to Policy H-460.925, which
31 encourages application of SCNT for uses other than human reproduction including medical therapeutic
32 procedures, and to Policy H-460.937, which recognizes that some areas of human embryo research (eg,
33 studies directed at improving the likelihood of a successful pregnancy, preimplantation genetic diagnostic
34 studies, and research on the fertilization process) may be acceptable for receiving federal funds (including
35 embryos created expressly for the purposes of research). Additionally, opposition to SCNT technology for
36 the purposes of biomedical research as noted in Policy H-460.917 may be inappropriate in light of recent
37 scientific data indicating that embryos created via SCNT technology can be a potent source for derivation
38 of pluripotent stem cells. Coupled with other new data indicating that stem cells derived from adult
39 sources may not be pluripotent, our AMA’s overarching support for the NBAC report must be revisited.
40 The pluripotency of stem cells derived from embryonic sources has repercussions in numerous areas of
41 biomedical research, including the possibility of developing antigenically identical tissues/organs for
42 treatment of a range of disorders (repair of damaged spinal cords, Parkinson’s disease, tissue/organ
43 transplantation); cancer research and treatment; and basic developmental and cellular biology, to name
44 only a few.

45 46 Background

47
48 Stem cells were first postulated to exist more than 40 years ago in the bone marrow of cancer patients¹ but
49 were not successfully isolated in vitro until approximately 20 years later.² Since that time, various aspects
50 of stem cell research have provided a rich source of scientific debate on issues ranging from their

1 therapeutic potential to the manner in which they can be isolated and genetically manipulated. Stem cells
2 are a unique population of cells that are characterized by their capacity for long-term self-renewal in
3 culture while retaining the ability to differentiate into specialized cells depending on intrinsic factors
4 (genetic) and the external microenvironment.³ They were initially thought to reside only in embryonic
5 tissue or adult tissue exhibiting self-renewing properties (eg, bone marrow and skin) but have been
6 recently identified in a variety adult tissues including brain and blood vessels.

7
8 Regardless of their origin, stem cells hold tremendous promise for treating a wide variety of human
9 diseases as well as answering some basic biological questions regarding development. Therapeutically,
10 stem cells can be used in regenerative medicine to replace diseased or damaged tissue. Disorders such as
11 diabetes, Parkinson's, and cardiovascular disease are ideally suited for such treatments since they involve
12 losses of specific cell populations that could be repaired using cell-based transplant therapies. The ability
13 to genetically manipulate stem cells means they can also be used as vehicles to deliver genes or proteins
14 in gene therapy. The potential to selectively differentiate large numbers of stem cells into specific cell
15 types makes them attractive for use in drug discovery and toxicology screening efforts as well. Finally,
16 stem cells represent a powerful new tool that can be used to define pathways and identify novel
17 components involved in lineage specification, cellular senescence, fertility/reproduction, and immune
18 rejection.

19 20 Embryonic Stem Cells

21
22 The first stem cells were isolated from a murine teratoma, a gonadal tumor composed of a mixture of
23 embryonal carcinoma (EC) cells and somatic tissue.⁴ Stem cells derived from these tumors were capable
24 of forming a variety of somatic and germ-line tissues, a capacity referred to as pluripotency. Much of
25 their initial value was based on their use as a model for cellular differentiation to define mechanisms that
26 regulate embryonic development and the formation of distinct cell lineages. Subsequent derivation of
27 stable EC cell lines derived from mice⁵ and humans⁶ enabled further identification of cell surface
28 antigens,⁷ transcription factors,⁸ and signaling pathways⁹ involved in differentiation of specific cell
29 lineages.

30
31 Because EC cells were derived from malignant carcinomas, efforts were initiated to isolate stem cells
32 from other sources that would exhibit more genetic stability. Two new populations of stem cells were
33 identified in murine embryos that were capable of forming cells derived from all 3 embryonic germ layers
34 (ectoderm, mesoderm, and endoderm). These new pluripotent stem cells were isolated from 2 different
35 embryonic sources. The first population, referred to as embryonic stem (ES) cells,¹⁰ were isolated from
36 the pre-implantation embryo (blastocyst) while the second was isolated from the genital ridge of the post-
37 implantation embryo (fetus) and called embryonic germ (EG) cells. Recently, human ES¹¹ and EG¹² cells
38 have been isolated and found to differ in a number of aspects including colony morphology, growth rates,
39 and surface antigens.¹³ Interestingly, prominent differences have also been observed between human and
40 murine ES cells, indicating they are not identical. For example, human ES cells can be induced to
41 differentiate into extraembryonic cell lineages (trophoblast) in culture while murine ES cells tend to form
42 more disorganized masses under similar conditions.¹⁴

43
44 Human ES cells are derived from a small group of about 30 cells that form the inner cell mass (ICM) of
45 the blastocyst-stage embryo. Embryos used to generate ES cells are derived from unused fertilized
46 oocytes (supernumerary embryos) donated with informed consent by individuals who have undergone in
47 vitro fertilization. Fertilized oocytes are cultured for approximately 5 to 6 days in vitro until they form a
48 hollow sphere of cells called a blastocyst. The ICM is harvested from blastocysts and plated in a Petri
49 dish onto a layer of mitotically inactivated murine embryonic fibroblasts (Figure 1). The fibroblastic
50 feeder layer provides a substrate for adhesion and secretes various nutrients that promote proliferation and
51 prevent differentiation. Concerns over possible contamination of human ES cells with murine viruses or

1 other cellular byproducts have prompted recent efforts to develop culturing methods that do not require
2 feeder layers.¹⁵ Individual cell colonies arising in these cultures are then separated and passaged
3 repeatedly until genetically identical (clonal) cell lines have been established. Clonal ES cell lines are
4 typically propagated for at least 6 months to ensure they remain undifferentiated, retain the ability to self-
5 renew, and exhibit genetic (karyotypic) stability. In addition, they are commonly tested for other
6 properties associated with embryonic cells (eg, expression of specific surface markers and transcription
7 factors) as well as pluripotency. A similar process is used to derive EG cell lines; however, the initial cell
8 mass used for culturing is isolated from the gonadal ridge of a 5- to 10-week-old fetus obtained from the
9 therapeutic termination of a pregnancy.

10
11 Much of the initial biology of ES and EG cells was established using stem cells derived from mammalian
12 sources, especially mice. Murine stem cells, while useful for providing therapeutic proof-of-concept in
13 pre-clinical animal models, are not suitable for clinical applications. Recent successes in isolating human
14 stem cells, however, provide the necessary tools for researchers to confirm their therapeutic potential. The
15 ability to isolate pluripotent human ES and EG cells has enabled several ES cell lines to be established.¹⁶
16 These lines exhibit properties consistent with stem cells including genetic stability after repeated passage
17 in culture (>8 months), expression of high levels of telomerase activity, displaying of surface markers
18 associated with undifferentiated stem cells, and pluripotency. These ES cell lines have also proven
19 invaluable for defining biological properties unique to human stem cells and developing methodologies
20 that will enhance their utility in cell-based therapies. For example, human cell lines have been used to
21 identify growth factors needed to direct differentiation of stem cells into specific cell types.¹⁷ In addition,
22 these lines have been used to develop protocols that allow genetic manipulation of stem cells using either
23 viral vectors¹⁸ or homologous recombination.¹⁹ More recently, a protocol was developed using single-
24 stranded oligodeoxynucleotides that enabled specific single base pair alterations to be introduced into the
25 genomes of ES cells.²⁰ Finally, culturing conditions were described recently for inducing human ES cells
26 to form trophoblasts and other extraembryonic cell lineages that will allow a better understanding of
27 placental development and function.²¹

28
29 Recent legislation restricting the use of human embryos in research has limited access of U.S. laboratories
30 to human ES cells. Currently, 71 human stem cell lines have been approved for use in federally funded
31 research.²² However, only 16 of these cell lines are available at the present time.²³ Unresolved issues
32 associated with licensing and patent rights have hindered the availability of many of these cell lines. In
33 addition, concerns are growing among scientists that many of the unavailable cell lines have not been
34 thoroughly characterized or developed to the degree required for research purposes. While the National
35 Institutes of Health (NIH) feels these cell lines are adequate for current basic research needs, serious
36 doubts remain that they will be sufficient to meet the needs of any future clinical trials for cell-based
37 therapies. Generation of additional human ES cell lines is still possible in U.S. laboratories as long as it is
38 not supported by federal funding but pending legislation could criminalize this type of research as well as
39 prevent importation of cell lines developed outside this country. Several countries including Israel,
40 Singapore, South Korea, Sweden, and the United Kingdom still permit the production of new human ES
41 cell lines from cloned embryos.²⁴ The fear among U.S. researchers is that much of the work conducted on
42 human stem cells will shift to these countries if federal legislation is approved banning the generation of
43 new ES cells in the United States.

44
45 The development of human ES cells represents a significant breakthrough in stem cell research.
46 Successful application of this technology in treating human disorders, however, will ultimately depend on
47 demonstrated efficacy in animal models and clinical trials. Therapeutic efficacy in these models will
48 require not only successful incorporation of transplanted cells into target tissue but also functional
49 integration into existing systems. Evidence suggesting that stem cells can meet these requirements is
50 found in several recent studies describing their use in treating various animal models of
51 neurodegenerative disorders. For example, human EC cell transplants were demonstrated to promote

1 significant functional recovery in a rodent model of spinal cord trauma.²⁵ In a separate study, human EC
2 cells delayed motor dysfunction in a mouse model of familial amyotrophic lateral sclerosis (ALS).²⁶
3 Recent work with human ES cells demonstrated that they could be differentiated into neural precursors in
4 vitro and then transplanted into neonatal mouse brain where they assimilated into various brain regions
5 forming both neurons and glial cells.²⁷

6
7 Murine ES cells have demonstrated efficacy in other animal models as well. In one study, cells
8 transplanted into rat spinal cord 9 days after traumatic injury were able to not only survive, migrate, and
9 differentiate into neurons and glia but also resulted in some functional recovery.²⁸ Finally, a recent study
10 demonstrated how murine ES cells can be genetically manipulated in culture to form a specific neuronal
11 cell type that when transplanted into a rat model of Parkinson's disease was able to repopulate a region of
12 the brain and provide functional recovery.²⁹ A similar protocol using genetic manipulation and subsequent
13 in vitro differentiation of murine ES cells was also used to restore function in a rodent model of
14 immunodeficiency.³⁰ A generalized summary of the research performed with human stem cells is
15 presented in the Table.

16 17 Somatic Cell Nuclear Transfer

18
19 One of the potential hurdles associated with the use of stem cells in therapeutic applications is the
20 problem of immune rejection. Although a number of human ES cell lines have been developed, their
21 clinical use as an allogenic transplant would presumably necessitate chronic immunosuppression of the
22 recipient. This concern prompted a recent study in which the cell surface expression of major
23 histocompatibility (MHC) antigens was characterized in human ES cell lines.³¹ While only low levels of
24 MHC-1 proteins were detected in undifferentiated cells, a significant induction of these proteins was
25 observed in differentiated cells following exposure to interferons, raising the question of whether a
26 similar phenomenon could occur following transplantation. To avoid this possible immune response, a
27 technique has emerged that may enable generation of stem cells that are specifically tailored for an
28 individual. The technique, somatic cell nuclear transfer (SCNT), involves reprogramming of a donor
29 oocyte so that it becomes immunologically compatible with a designated recipient. The process involves
30 removing the nuclear material from an unrelated donor oocyte (enucleation) and replacing it with the
31 nucleus from a recipient's somatic cell (nuclear transfer). The DNA injected into the enucleated oocyte
32 can be in the form of a nucleus (eg, from a fibroblast obtained via skin biopsy) or an entire cell, typically
33 a small specialized ovarian cell called a cumulus cell is used (Figure 2; left panel). The engineered oocyte
34 is then incubated in a culture dish with media that induce cell division (mitosis). The reprogramming of
35 an oocyte is a poorly understood process that involves activation of genes needed for early development
36 and suppression of genes associated with differentiation. The developing embryo is cultured in vitro for 5
37 to 6 days until the blastocyst is formed and then stem cells are harvested from the ICM.

38
39 SCNT was initially developed to generate clones for agricultural purposes and has been successfully used
40 to generate cloned cattle³² and sheep.³³ This technique was subsequently used for research purposes to
41 generate murine embryos³⁴ from which pluripotent ES cells were successfully derived.³⁵ Recently,
42 attempts have been made in a commercial laboratory (Advanced Cell Technology, Worcester, MA) to
43 produce ES cells derived from human embryos generated using SCNT technology.³⁶ In these experiments,
44 donated human oocytes were injected with either the nucleus from adult skin cells (fibroblast) or an
45 ovarian cumulus cell. The engineered oocytes all formed early-stage embryos but none progressed to the
46 stage where ICM cells could be harvested.³⁷ Differences in the organization of the mitotic spindle
47 apparatus in primates and humans indicate that SCNT techniques may have to be further optimized in
48 order to more efficiently produce human embryonic stem cells.³⁸

49
50 The most well publicized use of SCNT technology was the cloning of the sheep, Dolly.³⁹ She was the
51 product of an embryo generated by replacing the nucleus from an oocyte with the DNA from an adult

1 mammary cell. The sudden realization by the public that engineered embryos could be carried to term and
2 produce viable offspring raised concerns about possible misuse of SCNT to generate cloned human
3 beings (reproductive cloning). These concerns are based primarily on ethical issues since at the present
4 time, somatic cell cloning in mammals is a highly inefficient process with <1% of the embryos generated
5 by nuclear transfer surviving gestation. The reasons for this inefficiency remain unclear although
6 abnormalities in placental development appear to play a role.⁴⁰ Questions on the genetic stability of
7 embryos derived by SCNT have also arisen based on the premature death of Dolly and cloned mice.⁴¹
8 More recent studies analyzing gene expression in murine ES cells generated from SCNT suggest that
9 abnormalities affecting development and lifespan may result from inadequate nuclear reprogramming,
10 anomalies in gene imprinting, the process of SCNT itself, and the nature of the donor nucleus.⁴²

11
12 The inability to produce viable human embryos suitable for stem cell harvesting by SCNT has prompted
13 researchers to look for other ways to induce human oocytes to divide without being fertilized by sperm or
14 nuclear transfer. A technique known as parthenogenesis has demonstrated some limited success in certain
15 mammalian oocytes. This technique utilizes eggs harvested at a point in their maturation cycle when they
16 still retain a full set of genes and then subjects them to artificial stimulation to induce cell division. Stem
17 cells isolated from murine embryos generated by parthenogenesis have been shown to produce a variety
18 of tissues.⁴³ Parthenogenic activation of human oocytes has been described recently, but embryo
19 development ceased at a stage prior to ICM formation.⁴⁴ The inability to produce viable human embryos
20 would appear to involve only technical issues since this same laboratory has subsequently reported the
21 isolation of pluriopotent stem cells from nonhuman embryos generated by parthenogenesis.⁴⁵

22
23 SCNT technology is also being utilized in more basic research applications to understand molecular and
24 cellular events underlying human diseases. For example, a group at the Institute for Cancer/Stem Cell
25 Biology and Medicine at the Stanford University Medical Center has announced plans to generate human
26 and murine stem cell lines via SCNT that contain DNA mutations associated with specific human
27 diseases. These lines will allow scientists to study mechanisms by which disease-causing mutations affect
28 cellular function and development.

29 Adult Stem Cells

30
31
32 Stem cells were initially thought to be present only in embryonic tissue and adult tissue that exhibited a
33 capacity to regenerate, such as skin or liver. However, recent studies have demonstrated that stem cells
34 also exist in many types of adult tissue previously thought to contain only postmitotic cells incapable of
35 self-renewal. For example, stem cells have been isolated in several adult tissues including nervous,
36 adipose, placental, breast, muscle, and blood vessels. One of the main reasons these progenitors were so
37 difficult to detect was because that they exist in such small numbers and can remain quiescent (non-
38 dividing) for long periods of time until they are activated by injury or disease.

39
40 Unlike ES cells, the origin of adult stem cells is unknown and the question remains whether they are
41 independent populations or remnants of their embryonic counterparts. Additionally, controversy exists as
42 to whether stem cells isolated from certain adult tissues actually originated in these tissues or represent
43 temporary residents that were derived from a larger pool of circulating stem cells. For example, stem cells
44 isolated from adult murine muscle were initially reported to be capable of differentiating into cells from
45 all the major blood lineages.⁴⁶ Subsequent studies demonstrated that these stem cells were incapable of
46 forming myogenic cells when cultured in vitro, suggesting they had originated in the hematopoietic
47 system and therefore did not represent an actual population of pluripotent myogenic stem cells.⁴⁷

48
49 The notion of a highly plastic adult stem cell was initially contrary to the belief held by many in the field
50 that adult stem cells were limited to forming progeny of tissue from which they were derived. Recent
51 work indicates that adult stem cells might exhibit more plasticity and be capable of forming cells from

1 other tissues (multipotent). Stem cells isolated from tissues such as the brain,⁴⁸ skin,⁴⁹ and bone⁵⁰ have
2 been reported to contribute to various unrelated lineages (transdifferentiation). Unfortunately, in many of
3 these studies the inability to definitively demonstrate that stem cells differentiate into other cell types has
4 rendered these results controversial. More substantial evidence for the existence of multipotent stem cells
5 has emerged for mesenchymal stem cells derived from adult bone marrow (Figure 2; right panel). Murine
6 mesenchymal stem cells, referred to as multipotent adult progenitor cells (MAPCs), have been shown to
7 form cells from different tissues when grown in vitro and appeared to respond to environmental cues and
8 form tissue-specific cell types when engrafted into various adult tissues.⁵¹ For example, murine MAPCs
9 were recently demonstrated to transdifferentiate into functionally competent pancreatic islet cells when
10 systemically injected into irradiated mice.⁵² In light of the many controversial studies surrounding adult
11 stem cell plasticity, researchers in the field are now calling for more rigorous experimental standards be
12 applied to ensure that results are not artifacts of laboratory treatments. One such artifact that has gained
13 prominence of late is the ability of pluripotent stem cells to spontaneously fuse with differentiated cells in
14 culture and adapt a differentiated phenotype.⁵³ This phenomenon has been cited as a reasonable
15 alternative explanation for the plasticity observed in previous studies demonstrating that stem cells
16 isolated from the central nervous system (CNS) can form hematopoietic⁵⁴ and myogenic⁵⁵ cell lineages.
17 Efforts are now underway to determine how frequently cell fusion occurs in vivo and if stem cells are
18 directly involved in this process.

19
20 While adult stem cell plasticity remains controversial, the enthusiasm for potential use of these cells in
21 repairing diseased tissue remains resolute. The most prominent advances in therapeutic application of
22 adult stem cells to human disease is in the field of cardiovascular research. For example, adult bone
23 marrow stem cells have been reported to regenerate cardiomyocytes and induce angiogenesis in a rodent
24 model of myocardial infarction.⁵⁶ Results from 2 small clinical studies substantiated these results in
25 human patients who had suffered myocardial infarctions. Significant improvements in cardiac function
26 were observed 3 months after autologous transplant of mononuclear bone marrow cells into ischemic
27 heart tissue that were consistent with enhanced myogenesis⁵⁷ and angiogenesis.⁵⁸ Larger clinical studies
28 are needed to verify these results and answer such questions as the identity of the bone marrow cells
29 effecting repairs and the extent to which tissue was actually repaired.

30
31 The use of adult stem cells may avoid the ethical concerns associated with ES cells but does not
32 circumvent potential graft-versus-host rejection responses caused by using heterologous tissues. Recent
33 studies with human bone marrow stromal cells (BMSC) indicate that these cells may not be as
34 immunogenic as initially feared and therefore suitable for allogenic transplantation. In fact, in vitro
35 experiments suggest these cells actually suppress T-cell proliferation and thereby avoid/minimize
36 rejection.⁵⁹ The question remains whether these cells will retain these immunosuppressive properties once
37 they have differentiated in the target tissue. Work with nonhuman primate mesenchymal stem cells
38 confirmed that these types of adult stem cells exhibit characteristics suited for allogenic cell-based
39 therapies including ability to differentiate into multiple mesenchymal cell lineages,⁶⁰ undergo clinical
40 scale expansion, disseminate to a variety of tissues following systemic injection,⁶¹ and to be used as a
41 delivery vehicle for gene therapy.⁶²

42
43 Finally, the presence of stem cells in adult tissues such as the brain has raised the question of whether
44 their endogenous regenerative capacity can be harnessed to effect localized self-repair. This type of
45 therapeutic approach would involve inducing and/or enhancing intrinsic signals involved in directing the
46 migration, differentiation, and functional integration of stem cells into regions of the brain damaged by
47 disease or trauma. A recent study provided encouraging results for this approach. Infusion of growth
48 factors into the brains of rats following an ischemic event was found to augment the migratory and
49 proliferative capacities of neural stem cells in damaged brain regions.⁶³

Cord Blood Stem Cells

The controversies surrounding human embryo research have heightened interest in developing adult stem cells for therapeutic uses. Unfortunately, as noted above, adult cells do not appear to have the same plasticity as ES cells, potentially limiting their utility. Another nonembryonic source of multipotent stem cells gaining more attention in recent years is umbilical cord blood (UCB) cells. While these cells have been recognized as a convenient source of stem cells for many years,⁶⁴ the vast majority of clinical applications have involved treating hematopoietic disorders associated with malignant and nonmalignant cancers in both children and adults.⁶⁵ Their value in these types of therapeutic applications has increased even further lately with reports that hematopoietic stem cells can remain viable after being stored frozen for >15 years.⁶⁶

Recently, another population of stem cells has been identified in umbilical cords, specifically in the gelatinous connective tissue (Wharton's jelly) comprising the cord matrix.⁶⁷ The identity of these cells remains unclear but their ability to form neuronal lineages is similar to that described for mesenchymal stem cells, such as those derived from adult bone marrow stroma.⁶⁸ Interestingly, previous reports have demonstrated that peripherally administered human UCB cells preferentially migrate to the CNS and reduce neurological deficits in animal models of traumatic brain injury,⁶⁹ ischemic stroke,⁷⁰ and ALS.⁷¹ The ability of human UCB cells to delay the onset of neurodegenerative symptoms and ultimate death of transgenic ALS mice has prompted the Institute of Cellular Medicine in Atlanta, Georgia, to begin offering a similar therapy for ALS patients who otherwise have no treatment or cure available.⁷²

Related Advances in Stem Cell Research

In addition to the basic and clinical research being conducted directly on stem cells, a number of recent advances in related technologies have occurred that will facilitate their use in therapeutic applications. For example, a noninvasive imaging technique has been described for monitoring the migrational dynamics of stem cells after implantation into rodent brains. Magnetic resonance imaging (MRI) has provided sufficient temporal and spatial resolution in brain tissue to confirm that stem cells labeled with an MRI contrasting agent exhibited a directed migration toward an ischemic lesion located contralateral to the site of implantation.⁷³ The ability to observe the migration patterns of stem cell transplants in living tissue will undoubtedly lead to a better understanding of factors that direct their movement and induce differentiation.

A second advance associated with the stem cell field involves the use of endothelial stem cells as an index to assess cardiovascular risk in patients without known cardiovascular disease. High-resolution ultrasonic analysis of brachial arteries in 45 healthy men revealed an inverse correlation between the number of circulating endothelial progenitors and risk factors for cardiovascular disease.⁷⁴ These results not only suggest a novel use of stem cells but indicate that endothelial stem cells may help to maintain normal function in mature blood vessels and that loss of this function leads to abnormal vasoreactivity.

Finally, researchers at the University of Michigan Comprehensive Cancer Center recently announced they have isolated stem cells from human breast cancer tissue.⁷⁵ This discovery is unique in that stem cells have been isolated from blood-related cancers only and not from solid tumors. While these tumor-inducing stem cells comprise only a small percentage of the tumor, they may explain why metastatic breast cancers are able to regenerate following chemotherapy. Further characterization of these stem cells will allow therapies to be developed that will focus on their destruction.

1 Summary

2
3 The existence of stem cells in embryonic, postnatal, and adult tissues is well established. Numerous
4 questions remain on the origin of many of these stem cell populations and their ability to regenerate the
5 various cell lineages in the human body. One of the most prominent questions that needs to be addressed
6 is whether stem cells derived from adult tissues have the same regenerative potential as those derived
7 from embryonic sources. Until that question can be answered, most researchers agree that work must
8 continue on both embryonic and adult stem cells. Although science may appear at times to advance in
9 leaps and bounds, it relies on a thorough understanding of basic mechanisms before breakthroughs are
10 achieved. As demonstrated by the number of recent references in this report, the pace at which new
11 discoveries are being made in the stem cell field is rapidly accelerating. Studies describing the clinical
12 application of stem cell technology are starting to appear and continue to generate optimism that these
13 cells will one day play a major role in preventing and alleviating human disease. The need for SCNT to
14 generate immunologically compatible stem cells remains a subject of speculation given its inefficiencies
15 and ethical concerns. In addition, this need may be minimized if embryonic and adult stem cells prove to
16 be less immunogenic than initially thought. Most scientists agree that research must be conducted in
17 parallel on both adult and ES cells since each has advantages and disadvantages (eg, plasticity, longevity,
18 expansion, immune compatibility). For any particular disease, both embryonic and adult stem cells may
19 have to be evaluated to determine which is most efficacious. Clearly, the similarities and differences
20 between these types of stem cell populations must be better understood for their full potential to be
21 realized.

22 23 RECOMMENDATIONS

24
25 The Council on Scientific Affairs recommends that the following statements be adopted in lieu of
26 Resolution 511 (A-02) and the remainder of this report be filed.

27 28 1. Our AMA:

29 (1) supports biomedical research on multipotent stem cells (including adult and cord blood stem
30 cells); (2) supports the use of somatic cell nuclear transfer technology in biomedical research
31 (therapeutic cloning); (3) opposes the use of somatic cell nuclear transfer technology for the specific
32 purpose of producing a human child (reproductive cloning); (4) encourages strong public support of
33 federal funding for research involving human pluripotent stem cells; and (5) will continue to monitor
34 developments in stem cell research and the use of somatic cell nuclear transfer technology. (**New**
35 **HOD Policy**)

36 37 2. Policies H-460.917, H-460.925, and H-460.937 should be rescinded. (**Rescind HOD Policy**)

GLOSSARY OF TERMS

Adult stem cell: An undifferentiated cell found in differentiated tissue that can renew itself and (with certain limitations) differentiate to yield all the specialized cell types of the tissue from which it originated.

Blastocyst: A preimplantation embryo of about 150 cells. The blastocyst consists of a sphere made up of an outer layer of cells (trophectoderm), a fluid-filled cavity (blastocoel), and a cluster of cells on the interior (inner cell mass).

Bone marrow stromal cells (BMSC): A stem cell found in bone marrow that generates bone, cartilage, fat, and fibrous connective tissue.

Cell-based therapies: Treatment in which stem cells are induced to repair damaged or depleted adult cell populations or tissues.

Clone: A line of cells that is genetically identical to the originating cell; in this case, a stem cell.

Cumulus cell: Specialized cell that clings to ovum after ovulation that nurtures developing egg in ovary.

Differentiation: The process whereby an unspecialized early embryonic cell acquires the features of a specialized cell such as a heart, liver, or muscle cell.

Directed differentiation: Manipulating stem cell culture conditions to induce differentiation into a particular cell type.

Ectoderm: Upper, outermost layer of a group of cells derived from the inner cell mass of the blastocyst that forms skin nerves and brain.

Early embryo (pre-embryo): The term used to describe the preimplantation embryo that is biologically defined as the stages of development from fertilization until the

appearance to the primitive streak (approximately 14 days after fertilization).

Embryo: The developing organism from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus.

Embryonic germ (EG) cells: Cells found in a specific part of the embryo/fetus called the gonadal ridge that normally develop into mature gametes.

Embryonic stem (ES) cells: Primitive (undifferentiated) cells derived from inner cell mass of a blastocyst-stage embryo that have the potential to become a wide variety of specialized cell types (pluripotent).

Embryonic stem cell line: Embryonic stem cells, which have been cultured under in vitro conditions that allow proliferation without differentiation for months to years.

Endoderm: Lower layer of a group of cells derived from the inner cell mass of the blastocyst that forms lungs and digestive organs.

Feeder layer: Cells used in co-culture to maintain pluripotent stem cells. Cells usually consist of mouse embryonic fibroblasts.

Fertilization: The process whereby male and female gametes unite.

Fetus: A developing human from usually two months after conception to birth.

Genomic imprinting: Epigenetic modifications of DNA or proteins surrounding DNA (*e.g.* histones) that result in parent-specific expression or repression of genes in offspring.

Hematopoietic stem cell: A stem cell from which all red and white blood cells develop.

Homologous recombination: Technique used to introduce exogenous genetic material into recipient nucleus based on DNA homology.

In vitro: Literally, "in glass"; in a laboratory dish or test tube; an artificial environment.

In vitro fertilization (IVF): An assisted reproduction technique in which fertilization is accomplished outside the body.

Inner cell mass (ICM): The cluster of cells inside the blastocyst. These cells give rise to the embryonic disk of the later embryo and, ultimately, the fetus.

Long-term self-renewal: The ability of stem cells to renew themselves by dividing into the same non-specialized cell type over long periods (many months to years) depending on the specific type of stem cell.

Mesenchymal stem cells: Cells from the immature embryonic connective tissue. A number of cell types come from mesenchymal stem cells, including chondrocytes, which produce cartilage.

Mesoderm: Middle layer of a group of cells derived from the inner cell mass of the blastocyst; it gives rise to bone, muscle, and connective tissue.

Microenvironment: The molecules and compounds such as nutrients and growth factors in the fluid surrounding a cell in an organism or in the laboratory, which are important in determining the characteristics of the cell.

Multipotent: Ability of a single cell to develop into many different cell types of the body. Developmental potential of a multipotent stem cell is more restricted than pluripotent or totipotent stem cell.

Neural stem cell: A stem cell found in adult neural tissue that can give rise to neurons, astrocytes, and oligodendrocytes.

Parthenogenesis: Form of nonsexual reproduction in which unfertilized ovum is artificially induced to develop into an embryo.

Passage: A round of cell growth and proliferation in cell culture.

Plasticity: The ability of stem cells from one tissue to generate the differentiated cell types of another tissue.

Pluripotent: Ability of a single cell to develop into different cell types derived from each of the embryonic lineages (ectoderm, mesoderm, or endoderm) but cannot develop into an embryo on its own..

Proliferation: Expansion of a population of cells by the continuous division of single cells into two identical daughter cells.

Reproductive cloning: A term used to describe the process of generating a human embryo via somatic cell nuclear transfer for the specific purpose of creating a cloned human being.

Regenerative or reparative medicine: A treatment in which stem cells are induced to differentiate into the specific cell type required to repair damaged or depleted adult cell populations or tissues.

Somatic cell nuclear transfer (SCNT): Technique by which a somatic cell nucleus is transplanted into an ovum whose own nucleus has been removed (enucleated). Process also referred to as nuclear transfer or transplantation.

Stromal cells: Non-blood cells derived from blood organs, such as bone marrow or fetal liver, which are capable of supporting growth of blood cells in vitro. Stromal cells that make this matrix within the bone marrow are also derived from mesenchymal stem cells.

Subculturing: The process of growing and replating cells in tissue culture for many months.

Supranumerary embryo: Embryo originally generated for the purpose of assisted reproduction by in vitro fertilization (IVF) techniques but subsequently not used.

Surface markers: Surface proteins that are unique to certain cell types, which are visualized using antibodies or other detection methods.

Teratoma: A tumor composed of multiple tissues including tissues not normally found in organ in which it arises. Neoplasms frequently occur in ovary and testis. Produced experimentally in animals by injecting pluripotent stem cells, in order to determine the stem cells' abilities to differentiate into various types of tissues.

Therapeutic cloning: A term used to describe the process of generating a human embryo via somatic cell nuclear transfer for the specific purpose of obtaining stem cells for use in regenerative medicine.

Totipotent: Ability of a single cell to differentiate into any type of cell in the body (somatic, germ, or extraembryonic) and thus capable of forming a new organism (*e.g.* fertilized ovum).

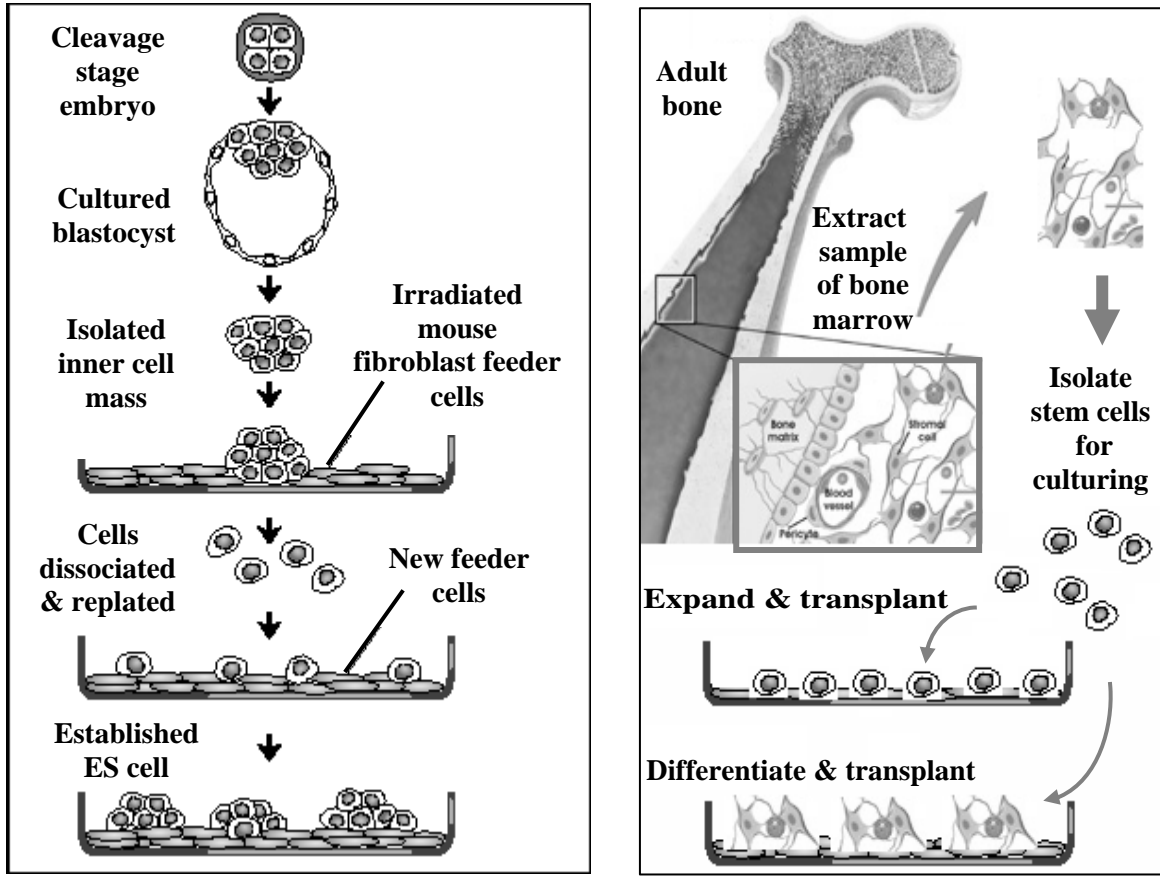
Transdifferentiation: The process by which stem cells from one tissue are able to differentiate into cells of another tissue.

Trophoblast: The extraembryonic tissue responsible for implantation, developing into the placenta, and controlling the exchange of oxygen and metabolites between mother and embryo.

TABLE: SUMMARY OF RESEARCH ON HUMAN STEM CELLS

	Embryonic carcinoma (EC) cells	Embryonic stem (ES) cells	Embryonic germ (EG) cells	Umbilical cord blood cells	Adult stem cells
Origin	Teratoma	Embryo	Embryo	Neonate	Adult
Differentiation potential	Pluripotent	Pluripotent	Pluripotent	Multipotent	Multipotent
Stable human cell lines established	Yes	Yes	No	No	No
Preclinical efficacy	Yes	Yes	Yes	Yes	Limited
Clinical efficacy	?	?	?	Limited	Limited

FIGURE 1. GENERATION OF EMBRYONIC (LEFT PANEL) AND ADULT (RIGHT PANEL) STEM CELLS



Adapted from Odorico et al., *Stem Cells* 2001;19:193-204.

Adopted from Stem cells: a primer
(<http://www.nih.gov/news/stemcell/primer.htm>)

FIGURE 2. SOMATIC CELL NUCLEAR TRANSFER

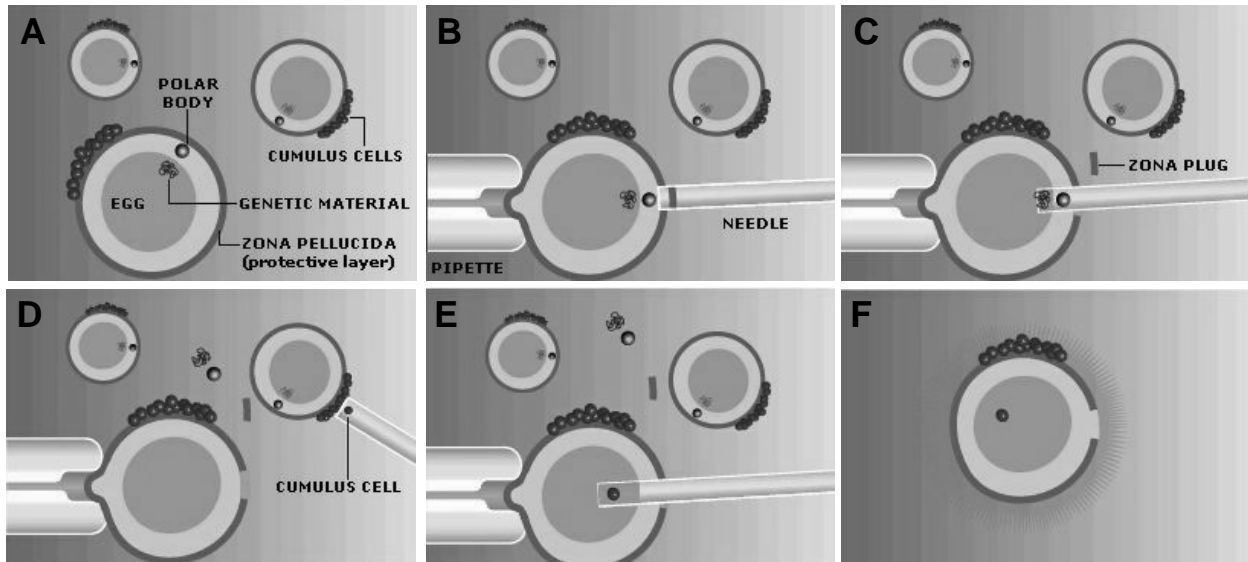


Figure taken from Cibelli et al., *Sci Am.* 2002;286:44-51.

- A:** Eggs are matured in a culture dish. Each egg has a remnant cell called the polar body and cumulus cells from the ovary attached to it.
- B:** A needle is used to drill through the zona pellucida and puncture the egg.
- C:** The zona plug is ejected and the needle is used to remove the polar body and egg's genetic material.
- D:** A cumulus cell from another egg taken up in the needle. Fibroblasts or their nuclei can also be used.
- E:** The cumulus cell is injected into the enucleated egg.
- F:** The injected egg is exposed to a mixture of chemicals and growth factors to activate division.

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APPENDIX – AMA POLICIES ON CLONING, STEM CELLS, AND SCNT

E-2.147 Human Cloning

"Somatic cell nuclear transfer" is the process in which the nucleus of a somatic cell of an organism is transferred into an enucleated oocyte. "Human cloning" is the application of somatic nuclear transfer technology to the creation of a human being that shares all of its nuclear genes with the person donating the implanted nucleus.

In order to clarify the many existing misconceptions about human cloning, physicians should help educate the public about the intrinsic limits of human cloning as well as the current ethical and legal protections that would prevent abuses of human cloning. These include the following: (1) using human cloning as an approach to terminal illness or mortality is a concept based on the mistaken notion that one's genotype largely determines one's individuality. A clone-child created via human cloning would not be identical to his or her clone-parent. (2) Current ethical and legal standards hold that under no circumstances should human cloning occur without an individual's permission. (3) Current ethical and legal standards hold that a human clone would be entitled to the same rights, freedoms, and protections as every other individual in society. The fact that a human clone's nuclear genes would derive from a single individual rather than two parents would not change his or her moral standing.

Physicians have an ethical obligation to consider the harms and benefits of new medical procedures and technologies. Physicians should not participate in human cloning at this time because further investigation and discussion regarding the harms and benefits of human cloning is required. Concerns include: (1) unknown physical harms introduced by cloning. Somatic cell nuclear transfer has not yet been refined and its long-term safety has not yet been proven. The risk of producing individuals with genetic anomalies gives rise to an obligation to seek better understanding of—and potential medical therapies for—the unforeseen medical consequences that could stem from human cloning. (2) Psychosocial harms introduced by cloning, including violations of privacy and autonomy. Human cloning risks limiting, at least psychologically, the seemingly unlimited potential of new human beings and thus creating enormous pressures on the clone-child to live up to expectations based on the life of the clone-parent. (3) The impact of human cloning on familial and societal relations. The family unit may be altered with the introduction of cloning, and more thought is required on a societal level regarding how to construct familial relations. (4) Potential effects on the gene pool. Like other interventions that can change individuals' reproductive patterns and the resulting genetic characteristics of a population, human cloning has the potential to be used in a eugenic or discriminatory fashion--practices that are incompatible with the ethical norms of medical practice. Moreover, human cloning could alter irreversibly the gene pool and exacerbate genetic problems that arise from deleterious genetic mutations, resulting in harms to future generations.

Two potentially realistic and possibly appropriate medical uses of human cloning are for assisting individuals or couples to reproduce and for the generation of tissues when the donor is not harmed or sacrificed. Given the unresolved issues regarding cloning identified above, the medical profession should not undertake human cloning at this time and pursue alternative approaches that raise fewer ethical concerns.

Because cloning technology is not limited to the United States, physicians should help establish international guidelines governing human cloning. (V) Issued December 1999 based of the report "The Ethics of Human Cloning" adopted June 1999.

H-140.930 The Ethics of Human Cloning

For the purpose of these guidelines, "somatic cell nuclear transfer" refers to the process in which the nucleus of a somatic cell of an organism is transferred into an oocyte from which the nucleus has been removed. "Human cloning" refers to the application of somatic nuclear transfer technology to the creation of a human being that shares all of its nuclear genes with the person donating the implanted nucleus. Human cloning, as defined in this report, does not include the use of somatic cells to create a pluripotent cell line that could, for instance, also be used for extra-uterine production of transplantable tissues without the creation of an entire being. Nor does it include the use of cloning technology for the production of human tissues or human proteins from transgenic mammals. This report does not address the issue of embryo or cloning research, stem cell research, embryo twinning, or embryo splitting.

- (1) In order to clarify the many existing misconceptions about human cloning, physicians should help educate the public about the intrinsic limits of human cloning as well as the current ethical and legal protections that would prevent abuses of human cloning. These include the following: (a) using human cloning as an approach to terminal illness or mortality is a concept based on the mistaken notion that one's genotype largely determines one's individuality. A clone-child created via human cloning would not be identical to his or her clone-parent. (b) current ethical and legal standards hold that under no circumstances should human cloning occur without an individual's permission. (c) current ethical and legal standards hold that a human clone would be entitled to the same rights, freedoms, and protections as every other individual in society. The fact that a human clone's nuclear genes would derive from a single individual rather than two parents would not change his or her moral standing.
- (2) Physicians have an ethical obligation to consider the harms and benefits of new medical procedures and technologies. Physicians should not participate in human cloning at this time because further investigation and discussion regarding the harms and benefits of human cloning is required. Concerns include: (a) unknown physical harms introduced by cloning. Somatic cell nuclear transfer has not yet been refined and its long-term safety has not yet been proven. The risk of producing individuals with genetic anomalies gives rise to an obligation to seek better understanding of -- and potential medical therapies for -- the unforeseen genetic consequences that could stem from human cloning. (b) psychosocial harms introduced by cloning, including violations of privacy and autonomy. Human cloning promises to limit, at least psychologically, the seemingly unlimited potential of new human beings and to create enormous pressures on the clone-child to live up to expectations based on the life of the clone-parent. (c) the impact of human cloning on familial and societal relations. The family unit would be different with the introduction of cloning, and more thought is required on a societal level regarding how to construct familial relations. (d) potential effects on the gene pool. Like other interventions that can change individuals' reproductive patterns and the resulting genetic characteristics of a population, human cloning has the potential to be used in a eugenic or discriminatory fashion -- practices that are incompatible with the ethical norms of medical practice. Moreover, human cloning could alter irreversibly the gene pool and exacerbate genetic problems that arise from deleterious genetic mutations, resulting in harms to future generations.
- (3) Two potentially realistic and possibly appropriate medical uses of human cloning are for assisting individuals or couples to reproduce and for the generation of tissues when the donor is not harmed or sacrificed. Given the unresolved issues regarding cloning identified above, the medical profession should forsake human cloning at this time and pursue alternative approaches that raise fewer ethical concerns. (4) Because cloning technology is not limited to the United States, physicians should help establish international guidelines governing human cloning. (CEJA 2, A-99)

H-460.917 Science, Policy Implications, and Current AMA Position Regarding Embryonic/Pluripotent Stem Cell Research and Funding

Our AMA: (1) encourages strong public support of federal funding for research involving human pluripotent stem cells (PSC); and (2) supports the recommendations of the National Bioethics Advisory Commission (NBAC) report, Ethical Issues in Human Stem Cell Research, September 1999. (CSA Rep. 15, I-99)

Commentary: Recommendations of the National Bioethics Advisory Committee (NBAC) Report were:

- Research involving the derivation and use of human embryonic germ cells (EGC) from fetal tissue cadavers should continue to be eligible for federal funding.
- Research involving the derivation and use of human embryonic stem cells (ESC) [i.e., PSC] from embryos remaining after infertility treatments should be eligible for federal funding.
- Federal agencies should not fund research involving the derivation or use of human ESC from embryos made solely for research purposes using IVF, or made using somatic cell nuclear transfer into oocytes.
- Prospective donors of embryos remaining after infertility treatments should receive timely, relevant, and appropriate information to make informed and voluntary choices.
- In federally funded research involving embryos remaining after infertility treatments, researchers may not promise donors that ESC derived from their embryos will be used to treat patient-subjects specified by the donors.
- Embryos and cadaveric fetal tissue should not be bought or sold.
- DHHS should establish a National Stem Cell Oversight and Review Panel to ensure that all federally funded research involving the derivation and/or use of human ESC/EGC is conducted in conformance with the ethical principles and recommendations contained in the NBAC report.
- Protocols involving the derivation of human ESC and EGC should be reviewed and approved by an institutional review board (IRB) or by another appropriately constituted and convened institutional review body prior to consideration by the Oversight and Review Panel.
- For privately funded research projects that involve ESC or EGC that would be eligible for federal funding, private sponsors and researchers are encouraged to adopt voluntarily the applicable recommendations of the report.
- The National Stem Cell Oversight and Review Panel should be chartered for a fixed period of time not to exceed five years.

H-460.925 Scientific Implications of Somatic Cell Transfer Technology

The AMA recommends a cessation of human somatic cell nuclear transfer research by both public and private sectors that involves the production of human beings. The AMA will work closely with the federal research funding agencies (NIH, NSF, NCI) and the FDA to determine if longitudinal animal studies indicate that nuclear transfer technology is safe and reproducible. The AMA encourages the applications of nuclear transfer technology for uses other than human reproduction by supporting basic science research programs that pursue medically therapeutic procedures such as organ and tissue transplantation. (Res. 11, A-98)

H-460.937 Cloning and Human Embryo Research

Our AMA: (1) supports the conclusions and recommendations of the Human Embryo Research Panel of the National Institutes of Health; (2) promotes efforts to maintain the 5-year moratorium on the cloning of human beings and prevent efforts to restrict current and future biomedical research unduly; (3) supports the efforts to develop an oversight mechanism similar to the Recombinant DNA Research Advisory Committee, affiliated with the National Institutes of Health, to review all human cloning experiments; and (4) supports efforts to establish a program for promoting the public understanding of science, and the understanding of social and philosophical issues by scientists. (BOT Rep. 13, A-95; Appended: CSA Rep.7, A-99)

Commentary: In September 1994, a National Institutes of Health (NIH) Human Embryo Research Panel released a report, which recommended that some areas of human embryo research be acceptable to receive federal funds, including embryos created expressly for the purposes of research, under certain limited conditions. The Panel determined that "sufficient arguments existed to support the permissibility of certain areas of research involving the preimplantation human embryo within a framework of stringent guidelines." The Panel identified three major factors that led to its affirmation of certain kinds of embryo research: (1) the promise of human benefit from embryo research is significant and carries great potential benefit to infertile couples, to families with genetic conditions, and to individuals who need effective therapies for a variety of diseases; (2) even though the preimplantation human embryo warrants serious moral consideration as a developing form of human life, it does not have the same moral status as infants and children, because it lacks most qualities considered relevant to the moral status of persons, including sentience (capacity for sensation or feeling), and there is a very high rate of natural mortality at the preimplantation embryo stage; and (3) without federal funding and regulation of preimplantation embryo research, this research will continue to be done in the private sector without consistent ethical and scientific scrutiny. The NIH Panel determined that embryos donated by couples in IVF programs are acceptable sources for research, whether the embryos are transferred to the uterus or not. The Panel also concluded that, because research involving the fertilization of eggs is required to answer crucial questions in reproductive medicine, it is ethically permissible to fertilize donated eggs expressly for research purposes. However, this should be allowed, they said, only if the research cannot be validated any other way, or when a compelling case is made that the research is required to validate a study that has potential outstanding scientific and therapeutic value.

The Panel identified a number of types of embryo research they considered to be acceptable for federal funding, including studies directed at improving the likelihood of a successful pregnancy, preimplantation genetic diagnosis studies, and research on the fertilization process. However, this research should be allowed only if it adheres to certain standards, including: it must be conducted by scientifically qualified individuals; it should involve the minimum number of embryos required; and it should be done with the informed consent of the donors of embryos or oocytes and sperm. The Panel recommended that all such embryo research proposals also be reviewed by a national advisory body for the first 3 years at a minimum.