

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Meslin, Eric (OD)" <MeslinE@od.nih.gov> ("Meslin, Eric (OD)" <MeslinE@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME: 21-JUL-1999 09:13:16.00

SUBJECT: RE: Weird subject heading

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ: UNKNOWN

TEXT:
yes we will.

Eric M. Meslin, Ph.D
Executive Director
National Bioethics Advisory Commission
6100 Executive Blvd. Suite 5B01
Rockville, Maryland 20892-7508
Tel: (301) 402-4242
Fax: (301) 480-6900
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<http://www.bioethics.gov>

-----Original Message-----

From: Rhetaugh [SMTP:rhetaugh@umich.edu]
Sent: Tuesday, July 20, 1999 5:11 PM
To: NBAC Members E-list
Subject: Re: Weird subject heading

Eric, I can't retrieve the Executive Summary. Would you please FAX it to 734-668-6103. I will be home most of Wednesday and will read and comment immediately upon receipt. I will be out of town Thursday through Sunday.

--On Tuesday, July 20, 1999, 2:24 PM -0400 "Meslin, Eric (OD)" <MeslinE@od.nih.gov> wrote:

> Trish has just mentioned to me that one of my previous emails containing
> the draft stem cell executive summary had an odd subject heading:
> "international research". I have no idea why that occurred.
>
> You all should have received the July 20 draft of the executive summary
> as a WORD attachment. Let me know if there are any difficulties opening
> or reviewing the document.
>

> Eric
>
> Eric M. Meslin, Ph.D
> Executive Director
> National Bioethics Advisory Commission
> 6100 Executive Blvd. Suite 5B01
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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Skirboll, Lana (OD)" <Skirboll@od1tml.od.nih.gov> ("Skirboll, Lana (OD)" <Skirboll@od1tml.od.nih.gov> [UNKNOWN])

CREATION DATE/TIME:22-JUL-1999 14:31:28.00

SUBJECT: Nature on stem cells

TO: "Flamberg, Gemma (OD)" <FlamberG@OD.NIH.GOV> ("Flamberg, Gemma (OD)" <FlamberG@OD.NIH.GOV> [UNKNOWN])
READ:UNKNOWN

TO: "O'Rourke, Pearl (OD)" <OrourkeP@OD.NIH.GOV> ("O'Rourke, Pearl (OD)" <OrourkeP@OD.NIH.GOV> [UNKNOWN])
READ:UNKNOWN

TO: "Smolonsky, Marc (OD)" <SmolonsM@OD.NIH.GOV> ("Smolonsky, Marc (OD)" <SmolonsM@OD.NIH.GOV> [UNKNOWN])
READ:UNKNOWN

TEXT:

Nature magazine July, 22, 1999

400, 301 (1999) ½ Macmillan Publishers Ltd.

<Picture>

White House cool on obtaining human embryonic stem cells

[WASHINGTON] The Clinton administration last week distanced itself from an impending recommendation by a presidential advisory commission that the government should fund both the derivation and the research use of human embryonic stem cells.

The recommendation is expected from the National Bioethics Advisory Commission (NBAC), which met in Cambridge, Massachusetts, last week to finalize a report to President Bill Clinton on the ethics of stem-cell research. The report may foment a Congressional debate that pits opponents of abortion against advocates of stem-cell research (see Nature 399, 292; 1999).

But the White House seems to be trying to avoid an open conflict. Advocates of stem-cell research hope it will yield cell and tissue therapies for diseases such as Parkinson's and juvenile diabetes. Opponents decry the research because the derivation of stem cells requires the destruction of embryos.

In a statement issued after NBAC met, the White House press secretary said the administration "recognizes that human stem-cell technology's potential medical benefits are compelling and worthy of pursuit, so long as the research is conducted according to the highest ethical standards".

But the statement added an implicit repudiation of the NBAC's recommendation that the government should finance the harvesting of stem cells from embryos left over after fertility treatments. It said that no legal action is necessary now "because it appears that human embryonic stem cells will be available from the private sector".

If the administration were to embrace a recommendation that it fund the collection of stem cells, it would have to lobby Congress to overturn or liberalize a law that bans government funding of research in which embryos are destroyed or discarded.

The government position is that federal funds may finance research on stem cells but not their harvesting, which must be done with private funds. This was delivered in a decision by the legal counsel of the Department of Health and Human Services in January (see Nature 397, 185; 1999).

But the authors of the ban on embryo research contest this interpretation. They may try to rewrite the ban to apply explicitly to stem-cell research when the appropriations bill to which it is attached is finalized this summer. If they do so, it is not clear which side would prevail in Congress.

Frank Young, a commissioner of the Food and Drug Administration under Ronald Reagan's presidency, said: "To say, on the one hand, that you cannot support the deliberate destruction of living human embryos to harvest their stem cells, but that you will, on the other hand, pour millions of taxpayer dollars in support of research that you know can only take place using materials derived from that destruction, is an exercise in sophistry, not ethics." Young was speaking on behalf of a group of abortion opponents called Do No Harm: The Coalition of Americans for Research Ethics.

But Joseph Cerquone, a spokesman for the Patients' Coalition for Urgent

Research, said his organization was "heartened" by the NBAC report and the White House reaction.

A spokeswoman for Harold Varmus, director of the National Institutes of Health, said last week that guidelines under which investigators funded by the agency may proceed with stem-cell work will soon be published. "We're being careful with them," she said, adding that they are already being discussed with the Department of Health and Human Services.

MEREDITH WADMAN

<Picture: Macmillan Magazines>Nature 376 1/2 Macmillan Publishers Ltd 1999
Registered
No. 785998 England.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Meslin, Eric (OD)" <MeslinE@od.nih.gov> ("Meslin, Eric (OD)" <MeslinE@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME:23-JUL-1999 16:59:06.00

SUBJECT: Stem Cell Update

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

A couple of you have called inquiring about our timetable, so I thought I'd transmit the latest news from the home office.

We have spent the past week working to finalize the Executive Summary.

Comments

from all commissioners who provided them have found their way into the text.

Harold has carefully reviewed and revised the text, and it is now in the hands

of our in-house editor who will spend the weekend going over it. By early next

week it should be complete. The Executive Summary and cover letter to the President will, if needed, constitute our report to the White House.

Beginning next week, staff will return to the chapters of the report itself and

begin revising the text as recommended at the Cambridge meeting. This will likely take a good deal of time, so I do not expect that commissioners

will see

a full revision for at least another 10 days or so (don't quote me on this, it

may take shorter or longer). Many commissioners have already sent in text for

some of the chapters. If you still have comments on any of them, send them in

electronically or by fax. We will probably try to send out chapters one at a

time as we think they are ready.

Have an enjoyable weekend.

Eric

Eric M. Meslin, Ph.D
Executive Director
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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: kramer <bkramers@worldnet.att.net> (kramer <bkramers@worldnet.att.net> [UNKNOWN])

CREATION DATE/TIME:26-JUL-1999 23:14:27.00

SUBJECT: Re: Stem Cell Update

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Meslin, Eric (OD) wrote:

>
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> a full revision for at least another 10 days or so (don't quote me on this, it
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> some of the chapters. If you still have comments on any of them, send them in
> electronically or by fax. We will probably try to send out chapters one at a
> time as we think they are ready.
>
> Have an enjoyable weekend.
>
> Eric
>
> Eric M. Meslin, Ph.D
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Eric-- We are leaving on vacation on July 31 and will return Aug. 16.

If any of the text is available before we leave I would love to see it.

Please fed ex, if time, or fax. thanks bette

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Hanna, Kathi (OD)" <HannaK@od.nih.gov> ("Hanna, Kathi (OD)" <HannaK@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME:29-JUL-1999 14:50:36.00

SUBJECT: chapter 1

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Attached for your review is the next version of chapter 1 of the stem cell report. We will be sending chapters out as they become available. Please try to get your responses and comments back on this chapter by Monday, August 2. As always, please call if you would like a fax or hard copy version. The person to call is Kerry Jo Lee at 301-402-4242.

Thanks,

Kathi

<<sc ch1 7-29.doc>>

- sc ch1 7-29.doc===== ATTACHMENT 1 =====

ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:

Unable to convert ARMS_EXT:[ATTACH.D60]ARMS29576411M.236 to ASCII,
The following is a HEX DUMP:

===== END ATTACHMENT 1 =====

CHAPTER 1

INTRODUCTION

Introduction [1]

In late 1998 three separate reports brought to the forefront the scientific and clinical prospects of human stem cell research. The term “stem cell” refers to those cells from which the different types of cells in a developing organism grow and which provide new cells throughout the organism’s life (Van Blerkom 1994). In the first two reports two independent teams of scientists described the first successful isolation of two types of human stem cells and their culture in the laboratory. Dr. John Gearhart and his colleagues at Johns Hopkins University derived a type of stem cell known as “human embryonic germ cells” (hereafter referred to as EG cells) from primordial gonadal tissue, which was obtained from cadaveric fetal tissue (Shamblott et al., 1998). In the second report, Dr. James Thomson and his co-workers at the University of Wisconsin derived embryonic stem cells (hereafter referred to as ES cells) from the blastocyst (~100-cell) stage of a early human embryos donated by couples that had received infertility treatment (Thomson 1998). The third report, which describes work funded by Advanced Cell Technology of Worcester, Massachusetts, appeared in the November 12, 1998 *New York Times*, and has not yet been published in a scientific journal or verified. In this report, the company claims that its scientists have made human somatic cells revert to the primordial state by fusing them with cow eggs to create a hybrid embryo. From this hybrid embryo a small clump of cells resembling human ES cells appear to have been isolated (Wade 1998).

Human Stem Cells [1]

Although there are many kinds of stem cells in the human body there is a hierarchy of types. Some stem cells are more committed, or differentiated, than are others. At the earliest stage of embryonic development, the cells of the blastomere are undifferentiated and each one is individually capable of generating a whole organism, a quality known as “*totipotency*.” In the next stage, ES cells, though no longer able to produce a whole organism, remain undifferentiated and retain the ability to develop into nearly any cell type of the body, a type of biological plasticity called “*pluripotency*.”

1 From this point, the ES cells branch out into many types; from each differentiated line
2 will develop all the specialized cells—e.g., heart, muscle, nerve, skin, or blood—that
3 constitute the tissues and organs of the body (Weiss et al., 1996).

4
5 The potential versatility of the ES and EG cells derived from the early-stage
6 embryo and cadaveric fetal tissue provides unusual scientific and therapeutic promise.
7 Because these cells have the ability to proliferate and renew themselves over the lifetime
8 of the organism, scientists have long recognized the possibility of using such cells to
9 generate a certain number of specialized cells or tissue, a possibility that could allow the
10 generation of new cells or tissue in response to injury or diseases such as Alzheimer's
11 disease, Parkinson's disease, heart disease, and kidney failure. Likewise, scientists regard
12 these cells as an important, perhaps essential, means for understanding the details of
13 human development and for developing life-saving drugs and other therapies. At the
14 same time the current source of these cells (the early stage embryo or cadaveric fetal
15 tissue) gives rise to important ethical considerations that must be taken into account.
16 Thus, the scientific reports of the successful isolation of these versatile cells have
17 simultaneously offered hope of new cures to debilitating and even fatal illness while
18 renewing debate about the ethics of research involving human embryos and cadaveric
19 fetal material.

20 21 **Ethical Issues [1]**

22 Within days of these scientific announcements President Clinton wrote to the
23 National Bioethics Advisory Commission with two requests: first that we consider the
24 implications of the purported cow-human fusion experiment and report back to him;
25 second that we “undertake a thorough review of the issues associated with human stem
26 cell research balancing all ethical and medical considerations” (Appendix A). We
27 responded to the President's first request in a letter November 20, 1998 that “any attempt
28 to create a child through the fusion of a human cell and a non-human egg would raise
29 profound ethical concerns and should not be permitted” (Appendix A). The reasons cited
30 for this were based on the same principals we relied on in our report to the President,
31 *Cloning Human Beings* (1997). We noted, however, that there is insufficient scientific

1 evidence at this time to determine whether the fusing of a human cell with the egg of a
2 non-human animal would result in a human embryo. And, if the resulting hybrid embryo
3 were to be used as a source of ES cells, it is not clear that those cells would be the same
4 in all respects to those obtained from a non-hybrid human embryo.

5
6 The scientific reports of the successful isolation and culture of ES and EG cells
7 have renewed a longstanding controversy about the ethics of research involving human
8 embryos and cadaveric fetal material. This controversy arises from sharply differing
9 moral views regarding elective abortion or the use of embryos for research. Indeed, an
10 earnest national and international debate continues over the ethical, legal, and medical
11 issues that arise in this arena. This debate represents both a challenge and an opportunity:
12 a challenge because it concerns important and morally contested questions regarding the
13 beginning of life, and an opportunity because it provides another occasion for serious
14 public discussion about important ethical issues. We are hopeful that this report will be
15 part of a dialogue that will foster increased public understanding about the relationships
16 between the opportunities that biomedical science offers to improve human welfare and
17 the limitations that may result because of important ethical obligations.

18
19 Wide agreement exists in our society that human embryos deserve respect as a
20 form of human life, but there is disagreement both on the form such respect should take
21 and what level of protection is owed at different stages of embryonic development.
22 Therefore, embryo research that is not therapeutic to the embryo itself is bound to raise
23 serious concerns for some about how to resolve the tensions between the ethical
24 imperative to cure diseases and the moral obligation to protect human life. For those who
25 believe that the embryo has the moral status of a person from the moment of conception,
26 research (or any other activity) that would destroy the embryo is wrong and should not
27 take place. For others, arriving at an ethically acceptable policy involves a complex
28 balancing of a number of important ethical concerns. Although this is a morally
29 controversial area, we should not lose sight of a broad area of consensus on which public
30 policy could, in part, be constructed.

1 In order to respond effectively and responsibly to the President's request to
2 consider issues related to human stem cell research and to "balance all medical and
3 ethical considerations," we determined that we must also consider certain aspects of the
4 broader issues of research using embryonic and fetal material. One reason for this is that
5 the nature of some of the ethical issues involved depends on the source of the stem cells
6 themselves. For example, ES cells can be derived from early embryos, which are,
7 however, destroyed in the process of ES cell derivation, an act that some people find
8 ethically unacceptable. The use of cadaveric fetal tissue to derive EG cell lines is
9 somewhat less controversial because the fetus is dead before the research is initiated and
10 because there is already in place a well-developed system of public oversight for certain
11 aspects of this research. In addition, recent accomplishments with nuclear transfer
12 techniques (somatic cell nuclear transfer) suggest that it might be possible to transfer the
13 nucleus from an adult cell into an oocyte, which under the right conditions could create
14 an embryo. However, The use of this technique to combine an animal oocyte with a
15 human nucleus raises additional issues about the nature of both the embryo produced and
16 the ethical issues involved. Thus, each source of material raises a unique set of scientific,
17 ethical, and legal distinctions.

18
19 We felt that it was especially important to take a broad perspective of the status of
20 the human embryo and fetal tissue in relation to biomedical research since it is likely that
21 science will uncover additional characteristics of the early *ex utero* human embryo or
22 fetal tissue that offer additional, important, and unique therapeutic possibilities, in
23 addition to those that may be derived from ES or EG cells. If these developments emerge,
24 all of the same ethical considerations that pertain to embryo research and fetal tissue
25 research in general would again arise.¹ In fact, the 1994 NIH Human Embryo Research
26 Panel² cited 13 areas in which embryo research could advance scientific knowledge or
27 could lead to important clinical benefits. One among these was "the isolation of
28 pluripotential embryonic stem cell lines for eventual differentiation and clinical use in
29 transplantation and tissue repair."

1 Recent scientific developments require us to update and review the important
2 work of previous U.S. bodies in addressing the role of the ethical complexities of human
3 embryo and fetal tissue research, particularly as it relates to the role of federally funded
4 research. In addition, new policy statements from other countries, such as those from
5 France and the United Kingdom, provide thoughtful new approaches that need to be
6 carefully considered. In responding to the President's request, therefore, we elected to
7 take a comprehensive approach that built on the work of these reflective efforts, both here
8 and abroad.

9
10 In our 1997 report, *Cloning Human Beings*, we addressed a specific aspect of
11 cloning, namely where genetic material would be transferred from the nucleus of a
12 somatic cell of an existing human being to an enucleated human egg with the intention of
13 creating a child. At the time, we did not revisit the issues surrounding embryo research,
14 although we began our discussions fully recognizing that any effort in humans to transfer
15 a somatic cell nucleus into an enucleated egg likely involves the creation of an embryo,
16 with the potential to be implanted *in utero* and developed to term. The Commission
17 recognized that ethical concerns surrounding issues of embryo research had recently
18 received extensive analysis and noted that under current law, the use of somatic cell
19 nuclear transfer to create an embryo solely for research purposes was prohibited in any
20 project involving federal funds. The President's request together with new developments
21 concerning human ES and EG cell research using embryos remaining after infertility
22 treatments or fetal tissue following elective abortion require that we reconsider the issue
23 of using these sources of cells for research purposes.

24
25 In this respect it is important to note that research on human embryos, or the
26 creation of human embryos for research purposes, is not only legal in the United States
27 but proceeds without any public oversight as long as 1) federal funds are not involved, 2)
28 FDA regulations do not apply, and 3) the laws of the particular state do not forbid such
29 activity. As a result, most of the public controversy surrounding such activities in the
30 United States has focused on whether or not it was appropriate for the federal government

1 to sponsor such research when it had great scientific merit and substantive clinical
2 promise. This is also the focus of this report.

4 **Framework for this Report [1]**

5 As noted above, President Clinton directed the Commission to conduct a thorough
6 review of the issues associated with human stem cell research balancing all ethical and
7 medical considerations. This approach—balancing or weighing difficult issues—often is
8 used in public policy discussions and has much to recommend it, particularly when such
9 balancing involves a serious consideration of different moral points of view, the state of
10 scientific and medical developments, and other factors. As discussed more fully in
11 chapter 4, some of the issues associated with research on human stem cells—the moral
12 status of the human embryo, for example—are especially sensitive and do not lend
13 themselves easily to this form of balancing. The Commission did not, for example, deem
14 the views of those who consider the fetus to have the moral status of a human person
15 from the moment of conception to have less (or more) moral weight than the views of
16 those who consider the fetus to lack this moral status. Similarly, we did not come to our
17 conclusions by simply balancing potential medical benefits against the potential harms
18 since the possibility of potential social benefits, by itself, is not a sufficient reason for
19 federal support of such morally contested research, particularly given the interest in stem
20 cell research in the private sector. Nor did we approach this issue based simply on
21 interpreting the existing legal environment. Instead, we combined, as thoughtfully as we
22 could, a number of different perspectives and approaches to this topic.

24 Our approach was as follows: through ongoing discussion and dialogue, informed
25 by scientists, philosophers, legal and religious scholars, members of the public, and
26 others, the commissioners developed their moral perspectives on the appropriateness of
27 the federal government sponsoring stem cell research involving the derivation and/or use
28 of ES and EG cells, principally focusing on the ethical and scientific issues. We
29 considered the sources of human EG and ES cells and the relevant moral differences that
30 ought to be taken into account in determining the acceptability of federal funding for the
31 derivation and/or use of cells from each of these sources. In this regard, we were assisted

1 by a number of commissioned papers (Fletcher 1999, Parens 1999; Knowles 1999; Siegel
2 1999; Kinner 1999; Brady 1999) each of which addressed different aspects of the
3 problem. We also benefited from the input of a group of religious scholars from diverse
4 faith traditions whose views within and across traditions reflected the diversity found
5 within the public as a whole. We then considered some associated ethical issues
6 including: voluntary informed consent, the just distribution of potential benefits from
7 stem cell research, and the commodification and sale of the body and its parts. Finally,
8 we considered how, and to what extent a mechanism of national oversight and review
9 would provide the necessary assurance that research, conducted responsibly and with
10 accountability, could go forward while protecting and valuing a number of deeply held
11 values. Some of these shared values were:

- 12
- 13 • Securing the safety and efficacy of clinical and/or scientific procedures, especially
- 14 where fundamental ethical and social issues are involved;
- 15 • Respecting human life at all stages of development; and
- 16 • Ensuring the responsible pursuit of medical and scientific knowledge.
- 17

18 **Definitions Used in this Report [1]**

19 We recognize the need to clearly define the terms that are central to the
20 understanding of this report. Because certain terms, such as “embryo” and “totipotent,”
21 are not always used in a precise or consistent manner, it is important to explain how the
22 Commission used this terminology.

23

24 The most important term to define is “embryo.” Canada's Royal Commission on
25 New Reproductive Technologies elucidated the confusion surrounding the term quite
26 well in their report *Proceed with Care* (1993):

27

28 There is a problem with terminology, as the term "embryo" is used in different
29 ways. In the language of biologists, before implantation the fertilized egg is
30 termed a "zygote" rather than an "embryo." The term "embryo" refers to the
31 developing entity after implantation in the uterus until about eight weeks after

1 fertilisation. At the beginning of the ninth week after fertilisation, it is referred to
2 as a "fetus," the term used until time of birth. The terms embryo donation,
3 embryo transfer, and embryo research are therefore inaccurate, since these all
4 occur with zygotes, not embryos. Nevertheless, because the terms are still
5 commonly used in the public debate, we continue to refer to embryo research,
6 embryo donation, and embryo transfer.

7
8 To be accurate when referring to the details of the developmental stages of an
9 entity, we use the following terminology: 1) the developing organism is a **zygote** during
10 the first week after fertilization; 2) the organism is an **embryo** during weeks 2 through 8
11 of development; and 3) the organism is a **fetus** from week 9 of development until the
12 time of birth. However, in other contexts, we will continue to use the broad terms
13 "embryo research," "embryo donation," and "embryo transfer" to refer to these uses of
14 zygotes since the public commonly uses these terms.

15
16 Since there are several sources for ES cells, we decided that it should give precise
17 names to each type of stem cell that would make clear the original source of the cells.
18 Therefore, cells derived from teratocarcinomas, malignant embryonic tumors, are called
19 **embryonal carcinoma (EC) cells**, cells derived from the inner cell mass of a blastocyst
20 (those cells within the conceptus that form the embryo proper) are called **embryonic**
21 **stem (ES) cells**, cells that are derived from primordial germ cells of embryos and fetuses
22 are called **embryonic germ (EG) cells**, and stem cells found in the adult organism are
23 called **adult stem (AS) cells**.

24
25 Two other terms that need explanation are "totipotent" and "pluripotent," since
26 there is disagreement within the scientific community over the meaning of these two
27 words. Some differentiate between the two terms by defining "totipotency" as the ability
28 to develop into a complete organism, and "pluripotency" as the ability to develop into all
29 of the cell types of an organism, but not capable of developing into an entire organism.
30 Others define "totipotent" as any cell that has the potential to differentiate into all cells of
31 a developing organism, and does not necessarily have to be able to direct the complete

1 development of an entire organism. These individuals would define “pluripotent” as any
2 cell that has the ability to differentiate into multiple (more than two) cell types. Instead of
3 entering into this debate and for the sake of clarity, we decided not to use this
4 terminology in this report, unless referring directly to work or statements of others in
5 which these words were originally included. Instead, this report uses descriptions of the
6 stage of development and the differentiation potential of cells to make clear to the reader
7 the types of cells being discussed.

9 **Organization of this Report [1]**

10 This report comes at a time when the Commission has just completed
11 deliberations about the use of human biological materials in research and submitted our
12 report (1999). Indeed, we recognized that in research involving such materials as DNA,
13 hair, and skin biopsies, there are a number of significant ethical issues that must continue
14 to be addressed by Institutional Review Boards, researchers and others; issues of privacy
15 and confidentiality, potential discrimination and stigmatization. As important as these
16 issues are—and they must be satisfactorily handled in order for research to proceed with
17 appropriate protections for human subjects—research on human stem cells, whether they
18 are obtained from fetal tissue following elective abortions or from tissue obtained from
19 embryos remaining after infertility treatment requires additional and perhaps even deeper
20 ethical reflection.

21
22 The Commission took as its primary task the development of a set of
23 recommendations that would provide advice on the appropriateness of permitting the
24 federal government to fund human ES and EG cell research and, where it was
25 appropriate, what sorts of constraints, if any, ought to be placed on such support.

26
27 The report first presents a summary of some of the key scientific issues involved
28 in stem cell research (Chapter 2). To place our analysis in context and to understand the
29 implications of making any new recommendations about the oversight and regulation of
30 research using fetal tissue and embryos, Chapter 3 describes the historical and current
31 status of laws and regulations governing the research use of these materials. Chapter 4

1 explores the various ethical issues surrounding the moral status of the embryo and
2 cadaveric fetal tissue and ethical concerns governing the acceptable use of these materials
3 in research. Chapter 5 offers our conclusions and recommendations regarding federal
4 sponsorship of research and of appropriate oversight activities in these ethically
5 controversial areas. Although this report primarily addresses the ethical issues associated
6 with the use of federal funds for research to derive and use ES and EG cells, we
7 recognize that considerable work in both of these areas will be conducted under private
8 sponsorship. Thus, our recommendations also may have implications for those working
9 in the private sector.

¹ For example, it has been generally recommended by most previous governmental and professional bodies that research on the *ex utero* preimplantation embryo should not be conducted beyond the 14th day post-fertilization. At 14 days the first stages of organized development begin, leading over the next few days to the first appearance of differentiated tissues of the body. The Commission concurs with this time limit on research involving the *ex utero* human embryo.

² The 1994 NIH Human Embryo Research Panel was asked to consider various areas of research involving the *ex utero* preimplantation human embryo and to provide areas that (1) are acceptable for Federal funding, (2) warrant additional review, and (3) are unacceptable for Federal support. The panel did not consider research involving *in utero* human embryos, or fetuses, since guidelines for such research already exist in the form of regulations.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Kathi E. Hanna" <khanna@chesapeake.net> ("Kathi E. Hanna" <khanna@chesapeake.net> [UNKNOWN])

CREATION DATE/TIME:30-JUL-1999 12:17:35.00

SUBJECT: Re: stem cell chapter 2

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
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----- Original Message -----

From: Elisa Eiseman <eiseman@rand.org>

To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>

Sent: Friday, July 30, 1999 1:03 PM

Subject: Re: stem cell chapter 2

> Kathi,

>

> The References and Glossary documents came through just fine, but for some

> reason, the chapter itself got converted, which means I can't open it.

> Would it be possible to resend just the Chap. 2 document to me.

>

> Thanks,

>

> -e

>

>

>> Attached please find a revision of chapter 2, with accompanying
>> references and glossary. We are preparing figures to go with this text
to

>> explain the various ways of deriving stem cells. They are not yet

>> available. Please contact the NBAC office (if you have not already
done

>> so) with instructions for alternative ways of receiving this

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August

>> 3. Thanks, Kathi Attachment converted: Macintosh HD:sc ch2
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- sc ch2 7-30.doc===== ATTACHMENT 1 =====
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CHAPTER 2: HUMAN STEM CELL RESEARCH AND THE POTENTIAL FOR CLINICAL APPLICATION

Introduction [1]

The stem cell is a unique and essential cell type found in animals. Many kinds of stem cells are found in the body, with some more differentiated, or committed, to a particular function than others. In other words, when stem cells divide, some of the progeny mature into cells of a specific type (heart, muscle, blood, or brain cells), while others remain stem cells, ready to repair some of the everyday wear and tear undergone by our bodies. These stem cells are capable of continually reproducing themselves and serve to renew tissue throughout an individual's life. For example, they continually regenerate the lining of the gut, revitalize skin, and produce a whole range of blood cells. Although the term "stem cell" commonly is used to refer to the cells within the adult organism that renew tissue (e.g., hematopoietic stem cells, a type of cell found in the blood), the most fundamental and extraordinary of the stem cells are found in the early-stage embryo (Van Blerkom 1994). These *embryonic stem* (ES) cells, unlike the more differentiated adult stem cells or other cell types, retain the special ability to develop into nearly any cell type. *Embryonic germ* (EG) cells, which originate from the primordial reproductive cells of the developing fetus, have properties similar to ES cells.

Because stem cells have the ability to proliferate and renew themselves over the lifetime of the organism—while retaining all of their multilineage potential—scientists have long recognized the potential of using such cells to generate a large number of specialized cells or tissue through amplification, a possibility that could allow the generation of new cells for the treatment of injury or disease. If, therefore, it was possible to control the differentiation of human ES cells in culture, the resulting cells could be used clinically to potentially help repair damage caused by such diseases as heart failure, diabetes, and certain neurodegenerative diseases.

In late 1998 three separate reports brought to the forefront the scientific and clinical prospects of human stem cell research. The first two reports, published by two independent teams

1 of scientists, describe the first successful isolation and culture in the laboratory of human ES and
2 EG cells. The research of both teams was supported by private funds from Geron Corp., a
3 biotechnology company in Menlo Park, CA. Dr. John Gearhart and his colleagues derived human
4 EG cells from primordial gonadal tissue, which was obtained from fetal tissue following elective
5 abortion (Shamblott et al., 1998). Dr. James Thomson and his co-workers derived human ES
6 cells from the blastocyst stage of early embryos donated by couples that had undergone infertility
7 treatment (Thomson and Marshall 1998). The ES and EG cells derived by each of these means
8 appear to be similar in structure, function, and potential, but it will take more research to fully
9 verify this claim (Varmus 1998). In addition, on November 12, 1998, the *New York Times*
10 reported that Advanced Cell Technology of Worcester, Massachusetts had carried out related
11 research, although the work has not yet been peer- reviewed, published, or verified. In this
12 report, the company claims to have made human cells revert to the primordial state by fusing
13 them with cow eggs, creating a hybrid embryo from which a small clump of cells resembling
14 human ES cells appear to have been isolated (Wade 1998).

15
16 The methodologies used by these investigators for deriving human ES and EG cells are
17 based on techniques used in mice since the early 1980s and, more recently, from non-human
18 primates and other animals. The isolation and culturing of these cells, however, open certain
19 avenues of important research and future clinical possibilities for the first time. At the most basic
20 level, the isolation of these cells allows scientists to focus on how ES and EG cells differentiate
21 into specific types of cells, with the goal of identifying the genetic and environmental signals that
22 direct their specialization into specific cell types. Such studies are ongoing using mouse stem
23 cells, but comparable studies with human cells will be needed to determine whether or not the
24 signals are the same. This research might, for example, lead to the discovery of new ways to treat
25 a variety of diseases including degenerative diseases, birth defects and cancer. This research
26 would build on investigations conducted over the last decade, in which laboratory animals have
27 been used to determine whether ES cells can be used to re-establish tissue in an adult organism
28 (Hall and Watt 1989; Corn et al., 1991; Hollands 1991; Diukman and Golbus 1992). Through
29 processes scientists are only beginning to understand, these primitive stem cells can be
30 stimulated to specialize so that they become precursors to different cell types, which may then be

used medically for replacement of tissues such as muscle, skin, nerve, or liver.

Box 2-A: Early Development of the Human Embryo

In humans, fertilization occurs in the fallopian tube. Fertilization, the union of an oocyte (egg) and sperm, results in the formation of the zygote. It takes 3-4 days for the zygote to travel down the fallopian tube to the uterus. As the zygote travels through the fallopian tube, several cell divisions (cleavages) occur.

The first division occurs about 36 hours after fertilization, when the zygote begins to cleave into two cells called blastomeres. At about 60 hours after fertilization, the 2 blastomeres divide again to form 4 blastomeres. At 3 days post fertilization, the 4 blastomeres divide to form 8 cells. Each blastomere becomes smaller with each subsequent division. In this early stage of development, all of the blastomeres are of equal size. These cells are unspecialized and have the capacity to differentiate into any of the cell types of the embryo as well as the essential membranes and tissue that will support the development of the embryo. Therefore, one or more of the blastomeres can be removed without affecting the ability of the other blastomeres to develop into a fetus. In fact, if an embryo separates in half at this early stage of development, identical twins—two genetically identical individuals—develop.

When the cell division reaches about 16 cells, the zygote is called a morula. It leaves the fallopian tube and enters the uterine cavity 3 to 4 days after fertilization. After reaching the uterus, the developing zygote usually remains in the uterine cavity an additional 4 to 5 days before it implants in the endometrium (uterine wall), which means that implantation ordinarily occurs on the 7th or 8th day following fertilization.

Cell division continues, creating a cavity known as a blastocoele in the center of the morula. With the appearance of the cavity in the center, the entire structure is now called a blastocyst. This first specialization event occurs just before the zygote attaches to the uterus, around 6 to 7 days after fertilization, when there are approximately 100 cells. This specialization involves the formation of an outer layer of trophoblast cells, which will give rise to part of the placenta, surrounding a group of about 20 to 30 inner cells (the inner cell mass or ICM) that remain undifferentiated. At this stage, these cells can no longer give rise to all of the cells necessary to form an entire organism, and therefore are not capable of developing into an entire

human being. In general, as cells further differentiate they lose the capacity to enter developmental pathways previously open to them.

As the blastocyst attaches to the uterus, the outer layer of cells secretes an enzyme, which erodes the epithelial uterine lining and creates an implantation site for the blastocyst. Once implantation has taken place, the zygote becomes an embryo. The trophoblast and sub-lying cells proliferate rapidly to form the placenta and the various membranes that surround and nourish the developing embryonic cells.

In the week following implantation, the inner cells of the blastocyst give rise to more of the placental tissue and eventually to a small disc of cells from which the fetus will develop. By 14 days the embryonic disc is about 0.5 mm in diameter and consists of about 2,000 cells. It is at this time that the first stage of organized development, known as gastrulation, is initiated, leading over the next few days to the first appearance of differentiated tissues of the body, including primitive neural cells. Gastrulation is the process by which the bilaminar (two-layered) embryonic disc is converted into a trilaminar (three-layered) embryonic disc and its onset at day 14 *in vivo* is marked by the appearance of the primitive streak. This is a region in which cells move from one layer to another in an organized way.

During the third week, the embryo grows to 2.3 mm long, and the precursors of most of the major organ systems begin to form. At the beginning of the third month the embryo becomes a fetus. During the 3rd to 9th month, the organ systems and tissues of the fetus continue to develop.

Stem Cell Types [1]

Scientists often distinguish between different kinds of stem cells depending on their origin and their potential to differentiate. Cells derived from malignant embryonic tumors, or teratocarcinomas, are called **embryonal carcinoma cells (EC cells)**, cells derived from the inner cell mass of a blastocyst embryo are called **embryonic stem cells (ES cells)**, and cells that are derived from precursors of germ cells from a fetus are called **embryonic germ cells (EG cells)**. In addition, stem cells can be found in the adult organism, for example, in bone marrow; they may possibly also be found in skin and intestine. These **adult stem (AS) cells** serve to replenish tissues where cells often have limited life span, such as the skin, intestine and blood. While there

1 is exciting new data that suggests that stem cells found in the adult organism are not restricted to
2 produce only cells from the tissue in which they reside (Bjornson et al., 1999), it is unlikely that
3 these cells are capable of differentiating into all cell types. In contrast, because human ES and
4 EG cells are believed to be capable of differentiating into all cell types they are likely to be of
5 clinical use in treating a variety of diseases, especially those for which organ-specific stem cells
6 are difficult to isolate and/or use.

7 **Embryonic Germ Cells [2]**

8 Primordial germ cells are the embryonic precursors of the sperm and ova of the adult
9 animal (Donovan 1998). The establishment of the germ line in the embryo involves the
10 separation of primordial germ cells from the somatic cells, proliferation of primordial germ cells,
11 migration of these cells to the gonad, and finally their differentiation to gametes (Donovan 1994).
12 Primordial germ cells are the only cells in the body that can give rise to successive generations,
13 while the somatic cells that form the body of the animal are destined for death once they start to
14 differentiate (Matsui 1998).

15
16 In culture, primordial germ cells can give rise to stem cells called embryonic germ (EG)
17 cells that are capable of differentiating into cells of multiple lineages (Donovan 1998). In the
18 body, primordial germ cells normally give rise to gametes, but sometimes if the developmental
19 process goes awry, they become embryonal carcinoma cells. Such cells are the stem cells of
20 teratomas, which are tumors containing derivatives of the three primary germ layers (Donovan
21 1998).

22
23 EG cells form embryoid bodies in culture, give rise to teratomas when introduced into
24 histocompatible animals, and form germline chimeras when introduced into a host blastocyst
25 (Donovan 1998). The derivation of EG cells directly from primordial germ cells represents a
26 mechanism to study some aspects of primordial germ cell development such as imprinting and
27 differentiation (Donovan 1994). At the same time it may be difficult to get an adequate supply of
28 fetal tissue with the appropriate properties to provide the relevant cell lines needed for both
29 research and clinical needs.

Embryonic Stem Cells [2]

In mammalian embryonic development, cell division gives rise to differentiated daughter cells that eventually comprise the mature animal. As cells become committed to a particular lineage, or cell type, a progressive decrease in developmental potential presumably occurs. Early in embryonic development (until about 16 cells), each cell of the early cleavage-stage embryo has the developmental potential to contribute to any embryonic or extraembryonic cell type (Winkel and Pedersen 1988). However, by the blastocyst stage, cells of the trophectoderm are irreversibly committed to forming the placenta and other trophectoderm lineages (Winkel and Pedersen 1988). By six to seven days post fertilization, the inner cell mass has divided to form two layers, which give rise to the embryo proper, and extra-embryonic tissues (Gardner 1982).

Although the cells of the inner cell mass are precursors to all adult tissues, they can only proliferate and replace themselves in the intact embryo for a limited time before they become committed to specific lineages (Thomson and Marshall 1998). ES cells are derived from cells of the inner cell mass. Once they are placed in the appropriate culture (laboratory growth) conditions, these cells seem to be capable of extensive, undifferentiated proliferation *in vitro*, and maintain the potential to contribute to all adult cell types (Evans and Kaufman 1981; Martin 1981).

While these embryonic cells are “stem cells,” they differ substantially from the stem cells found within the fully developed, or adult organism (see below). Most importantly, ES cells are highly proliferative, both in the embryo as well as in culture, while some stem cells of the adult can be almost totally quiescent, and may be more difficult to maintain and expand in culture (Van Blerkom 1994). Therefore, it appears that if stem cells were someday to be used for the treatment of disease, it might be advantageous to use ES cells for some disorders.

Sources of Human Embryonic Stem Cells [3]

ES cells are derived from early embryos in culture. Because of moral concerns, including respect for human dignity, this report distinguishes between three sources of ES cells: 1) embryos created by *in vitro* fertilization for infertility treatments that were not implanted because they

1 were no longer needed by the couple; 2) embryos created expressly for research by *in vitro*
2 fertilization; and 3) embryos resulting from somatic cell nuclear transfer (SCNT), or other
3 cloning techniques. SCNT has opened the possibility of an alternative way to create ES cells. If
4 the nucleus is removed from an immature egg (oocyte) and a mature diploid nucleus is inserted,
5 the resulting cell will divide and develop with many characteristics of an embryo. In animal
6 experiments when an SCNT-derived embryo is transferred to a surrogate mother, a successful
7 pregnancy can be established. This was the technique used to generate the now famous cloned
8 sheep Dolly. If instead of being transferred to a surrogate, the SCNT-derived embryo is kept in
9 culture, is allowed to divide, and is then dissociated, ES cells can be derived. The potential
10 advantage of using SCNT technology to create ES cells is that a somatic cell from an individual
11 can be used to create ES cells that are completely compatible with that individual's tissue type. If
12 cells or tissues are generated from these ES cells for transplant into a person, this tissue type
13 compatibility may avoid many of the problems associated with tissue graft rejection currently
14 encountered in clinical treatment of a variety of diseases.

15
16 The use of SCNT into an oocyte has been criticized as an asexual or "unnatural" way of
17 creating a human embryo. However, it is important to distinguish the technique of SCNT from
18 the type of cell that is created, that is, SCNT techniques might also be used with recipient cells
19 other than oocytes. For example, ES cells with matched tissue types for transplant might be
20 generated by SCNT into an enucleated ES cell.¹ This possibility has not yet been explored
21 experimentally, but it may be less morally problematic to many as the cell created would not be
22 an embryo with the potential to continue development.

23 **Stem Cells Found in the Postnatal and Adult Organism [2]**

24 In the adult mammal, cell division occurs in order to maintain a constant number of
25 terminally differentiated cells in tissues where cells are lost due to injury, disease, or natural cell
26 death. Cells with a high turnover rate are replaced through a highly regulated process of
27 proliferation, differentiation, and apoptosis (programmed cell death) from relatively
28 undifferentiated stem cells, or precursor cells (Thomson and Marshall 1998). The best known
29 example of an adult stem cell is the hematopoietic stem cell found in bone marrow, which is

1 responsible for the production of all types of blood cells (Iscoe 1990). Other examples of stem
2 cells include the skin epithelium and the epithelium of the small intestine (Hall and Watt 1989).
3 In the human small intestine, for example, approximately 10^{11} (100 billion) cells are shed and
4 must be replaced daily (Potten and Loeffler 1990). These tissues contain subpopulations of
5 dividing stem cells that generate replacements for the relatively short-lived, terminally
6 differentiated cells. Much of the debate in the stem cell field revolves around determining the
7 breadth of the potential of these cells; can they give rise to all cell types of that organ or only a
8 restricted few?

9
10 The successful cloning of Dolly the sheep demonstrated that even somatic cells are
11 capable of forming every cell of an organism after nuclear transfer into an oocyte (Wilmot, et al.,
12 1997). Preliminary studies of stem cells obtained from various systems of the adult organism
13 suggest that in some cases the reactivation of dormant genetic programs may not require nuclear
14 transfer or experimental modification of the genome. Although research in this area is
15 preliminary, this particular class of stem cells, i.e. adult stem cells, might be able to differentiate
16 along several, but probably not all, cell lineages in response to an appropriate pattern of
17 stimulation.

18 **Neural Stem Cells [3]**

19 It has been recognized for a number of years that transplantation of fresh fetal tissue into
20 the diseased adult brain may be a promising therapy for neurodegenerative disorders, and has
21 recently been shown to be effective in younger patients with Parkinson's disease (reported by
22 Curt Freed to American Academy of Neurology, April 21, 1999). This technique has several
23 disadvantages, however, such as the necessity of timing the surgery to the availability of large
24 amounts of fresh fetal tissue, the need to quickly screen for infectious diseases, and the limited
25 amount of donor fetal tissue available (Bjorkund 1993; Cattaneo and McKay 1991). By
26 developing techniques to culture and expand primary fetal neural cells before transplantation,
27 some of the problems of using fresh tissue may be eliminated. In addition, it may be possible to
28 direct cultured cells to develop along certain lineages or to express specific genes before they are

transplanted, so that, for example, dopamine-producing cells could be selectively grown to treat Parkinson's disease (Cattaneo and McKay 1991; Snyder 1994).

Indeed, it has already been demonstrated that neural stem cells are capable of gene (Snyder et al., 1995) and cellular (Snyder et al., 1997; Rosario et al., 1997; Yandava, Billinghamurst, and Snyder 1999) replacement in models of neural disease. Interestingly, in many of these experiments one stable clone of mouse neural stem cells could be used from individual to individual, strain to strain, and disease to disease, regardless of recipient age within the species, without immunorejection or the need for immunosuppression, suggesting that unique immune qualities may exist within stem cells, which might allow them to be “universal donors.” Moreover, the possibility exists that a good deal of instructive cues for differentiation may actually come from interaction with damaged CNS tissue itself.

The embryonic nervous system arises from the ectoderm. The first cell type to differentiate from the uncommitted precursor cells is the neuron, followed by the oligodendrocyte, and then the astrocyte (Frederiksen and McKay 1988). Recently, Angelo Vescovi, a neurobiologist at the National Neurological Institute Carlo Besta in Milan, Italy, and his colleagues reported that neural stem cells, which give rise to the three main types of brain cells, can also become blood cells when transplanted into mice whose own blood-forming tissue, the bone marrow, has been mostly destroyed (Bjornson et al., 1999). The study did not explain what caused the neural cells to turn into blood cells, but the investigators speculate that the neural cells might be responding to the same signals that normally stimulate the few remaining blood stem cells to reproduce and mature after irradiation wipes out most of the bone marrow (Strauss 1999). Although this research is preliminary and has not yet been conducted using human cells, it opens the possibility of using neural stem cell transplants to treat human blood cell disorders such as aplastic anemia and severe combined immunodeficiency—an appealing idea, as bone marrow stem cells do not replenish themselves well in laboratory cultures. However, the problem of access to such cells in humans remains, as such cells have to be obtained from the brain, an invasive and risky procedure. This research also opens up the possibility that other apparently restricted adult stem cells may retain the ability to differentiate

1 into several different types of cells if exposed to the right external environment. However,
2 further research is required in this area.

4 **Mesenchymal Stem Cells [3]**

5 Human mesenchymal stem cells, which are present in adult bone marrow, can replicate as
6 undifferentiated cells and have the potential to differentiate to lineages of mesenchymal tissues,
7 including bone, cartilage, fat, tendon, muscle, and marrow stroma (Pittenger et al., 1999). In a
8 recent experiment, cells that have the characteristics of human mesenchymal stem cells were
9 isolated from marrow aspirates of volunteer donors. Individual stem cells were identified that,
10 when expanded to colonies, retained their multilineage potential. This shows that isolated
11 expanded human mesenchymal stem cells in culture will differentiate, in a controlled manner, to
12 multiple—but limited—lineages. It is speculated that these particular adult stem cells could be
13 induced to differentiate exclusively into the adipocytic, chondrocytic, or osteocytic lineages,
14 which might be used to treat various bone diseases.

16 The specific environmental cues to initiate the proliferation and differentiation of these
17 cells are not understood (Pittenger et al., 1999). The ability to isolate, expand, and direct the
18 differentiation of such cells in culture to particular lineages, however, provides the opportunity to
19 study events associated with cell commitment and differentiation. The human mesenchymal stem
20 cells isolated by Pittenger and colleagues appear to have the ability to proliferate extensively, and
21 maintain the ability to differentiate into certain cell types in culture. Their cultivation and
22 selective differentiation should provide further understanding of this important progenitor of
23 multiple tissue types and the potential of new therapeutic approaches for the restoration of
24 damaged or diseased tissue (Pittenger et al., 1999).

25 **Animal Models [1]**

26 ES cells were first derived from mouse embryos, and have become the principal model
27 system for the study of these cells (Evans and Kaufman 1981; Martin 1981). More recently, cells
28 with some properties of ES cells have been derived from cows, pigs, rats, sheep, hamsters,
29 rabbits and primates (reviewed in Pedersen, 1994; see Table 2-1). However only in cows, pigs

and rats did these ES cells contribute to a chimeric animal and in none of these was there germline contribution of the ES cell lineage (ref?). This germ line contribution is the most stringent criterion for ES cells.

Table 2-1. Stem Cells Isolated from Mammals

Species	References
Mouse	Evans and Kaufman, 1981 Martin, 1981
Rat	Iannaccone et al., 1994
Hamster	Doetschman, Williams, and Maeda 1988
Mink	Sukoyan et al., 1992 Sukoyan et al., 1993
Rabbit	Cole et al., 1965a, b Moreadith and Graves, 1992 Giles et al., 1993 Graves and Moreadith, 1993
Sheep	Handyside et al., 1987 Piedrahita, Anderson, and Bondurant 1990 Notarianni et al., 1990
Pig	Piedrahita et al., 1988 Evans et al., 1990 Notarianni et al., 1990 Piedrahita et al., 1990 Hochereau-de Reiviers and Perreau, 1993 Talbot et al., 1993 Wheeler 1994 Shim et al., 1997
Cow	Evans et al., 1990 Saito, Strelchenko, and Niemann, 1992 Strelchenko and Stice, 1994 Cibelli et al., 1998
Common Marmoset	Thomson et al., 1996
Rhesus Monkey	Thomson et al., 1995
Human	Bongso et al., 1994 Shamblott et al., 1988 Thomson et al., 1998

Mouse Embryonic Stem Cells [2]

ES cells were first isolated from mouse blastocysts in 1981 (Evans and Kaufman 1981;

1 Martin 1981). Blastocysts were placed in culture and allowed to attach to the culture dish so that
2 trophoblast cells spread out, while the undifferentiated inner cells (the inner cell mass) continued
3 to grow as a tight, but unorganized, cluster. Before the inner cell mass developed into the
4 equivalent of the embryonic disc, it was drawn up into a fine pipette, dissociated into single cells,
5 and dispersed into another dish with a rich culture medium. Under these circumstances, the
6 dissociated cells continued to grow rapidly for an extended period of time.

7
8 Mouse ES cells cannot become organized into an embryo by themselves or implant into
9 the uterus if placed there. However, if the cells are injected back into a new blastocyst, they can
10 intermingle with the host inner cell mass to make a chimera and take part in normal
11 development, eventually contributing to all the tissues of the adult mouse, including nerve,
12 blood, skin, bone, and germ cells (reviewed in Robertson and Bradley, 1986). This indicates that
13 mouse ES cells have not lost the capacity to give rise to specialized tissues, but they will not do
14 so unless placed in the right environment.

15
16 The ability of mouse ES cells to enter the germ line in chimeras allows the introduction of
17 specific genetic changes into the mouse genome and offers a direct approach to understanding
18 gene function in the intact animal (Rossant, Bernelot-Moens, and Nagy, 1993). Using the
19 technique of homologous recombination in which a gene is either modified or disabled
20 ("knocked out"), mouse ES cells can be derived that contain specific gene alterations. These
21 genetically altered cells can then be used to form chimeras with normal embryos and
22 subsequently bred to generate a mouse lacking one specific gene or containing an extra or altered
23 gene.

24
25 Mouse ES cells have also been extremely useful as models of the early differentiation
26 events that take place during the development of mammalian embryos (reviewed in Pedersen,
27 1994). For example:

- 28 • When mouse ES cells were allowed to differentiate in culture, beating heart cells formed
29 spontaneously, providing a model for cardiac-specific gene expression, and the development
30 of cardiac muscle and blood vessels (Robbins et al., 1990; Wobus, Halukat, and Heschler,

1 1991; Chen and Kosco, 1993; Doetschman et al., 1993; Miller-Hance et al., 1993;
2 Muthuchamy et al., 1993).

- 3 • Blood formation will occur spontaneously in ES cell-derived embryoid bodies, and can be
4 augmented by modifying the culture conditions (reviewed in Snodgrass, Schmitt, and Bruyns
5 1992). Therefore, hematopoietic stem cells have been studied extensively to determine the
6 conditions for differentiation, survival, and proliferation of blood cells.
- 7 • Several studies have highlighted the importance of growth and differentiation factors in the
8 regulation of mammalian development. For example, the maintenance of mouse ES cells in
9 an undifferentiated state was found to require the presence of leukemia inhibitory factor
10 (LIF), a differentiation-inhibiting factor (reviewed in Fry, 1992). Other studies have found
11 several growth and differentiation factors to be important in ES cell development and
12 differentiation, including activins, colony-stimulating factor, erythropoietin, basic fibroblast
13 growth factor, insulin-like growth factor 2, interleukins, parathyroid hormone-related peptide,
14 platelet-derived growth factor, steel factor, and transforming growth factor β (reviewed in
15 Pedersen, 1994).
- 16 • In mid-gestation embryos and the adult mouse, only one parental allele of imprinted genes is
17 expressed. However, studies have suggested that there is limited relaxation of imprinting in
18 ES cells so that both maternal and paternal alleles are expressed (reviewed in Pedersen,
19 1994).

20 By understanding the mechanisms responsible for growth and differentiation in
21 embryonic development, it may then be possible to attempt to regulate the differentiation of ES
22 cells along specific pathways. The knowledge gained from these types of studies could someday
23 lead to the effective treatment of certain important human diseases.

24
25 Historically, because of its well-defined genetics, short gestational times, ease of
26 cultivation, and large litters, the mouse has been one of the primary models for the study of
27 mammalian embryonic development. However, there are several differences between early
28 mouse development and early human development, including differences in:

- 29 • the timing of embryonic genome expression (Braude, Bolton, and Moore 1988);

- the formation, structure, and function of the fetal membranes and placenta (Luckett 1975, 1978; Benirschke and Kaufmann 1990); and
- formation of an egg cylinder in the mouse as opposed to an embryonic disc in humans (O'Rahilly and Muller 1987; Kaufmann 1992).

Therefore, other animal models as well as new models that would directly allow the study of human embryonic development are crucial for our comprehension of early human development and for understanding the growth requirements of human stem cells of specific lineages.

Bovine Embryonic Stem Cells [2]

The first bovine ES-like cells were reported by Saito et al. (Saito, Strelchenko, and Niemann 1992). More recently, transgenic bovine ES-like cells were derived by using nuclear transfer of fetal fibroblasts to enucleated bovine oocytes (Cibelli et al., 1998). This technique involved introducing a marker gene into bovine fibroblasts from a 55-day old fetus and then fusing the transgenic fibroblasts to enucleated oocytes to produce blastocyst-stage nuclear transplant embryos (Cibelli et al., 1998). ES-like cells were then derived from these embryos and used to create chimeric embryos. When reintroduced into preimplantation embryos, these transgenic ES-like cells differentiated into derivatives from the three embryonic germ layers, ectoderm, mesoderm, and endoderm (Cibelli et al., 1998). Bovine ES cells would be very useful in agricultural production of transgenic cows and may also have the potential for generating tissues and organs for use in cross species (xenotransplantation) to treat human diseases.

Primate Embryonic Stem Cells [2]

Primate ES-like cells have been derived from both the rhesus monkey (Thomson et al., 1995) and the common marmoset (Thomson et al., 1996). When allowed to grow to confluence and pile up, both marmoset and rhesus ES cells spontaneously differentiate into more complex structures, including cardiac muscle, neurons, endoderm, trophoblast, and numerous unidentified cell types (Thomson and Marshall 1998).

Essential characteristics of these primate ES-like cells include: 1) derivation from the preimplantation or peri-implantation embryo; 2) prolonged undifferentiated proliferation; and 3)

1 stable developmental potential to form derivatives of all three embryonic germ layers even after
2 prolonged maintenance in culture (Thomson and Marshall 1998). In addition, while mouse ES
3 cells rarely contribute to trophoblast in chimeras (Beddington and Robertson 1989), primate ES
4 cells differentiated into all three germ layers and trophoblast-like cells (Thomson and Marshall
5 1998). Furthermore, some primate ES cell lines have maintained a normal karyotype through
6 undifferentiated culture for at least two years, sustained a stable developmental potential
7 throughout this culture period, and maintained the potential to form trophoblast *in vitro*
8 (Thomson et al., 1995, 1996).

10 Although there is some variation between species, nonhuman primate ES cell lines seem
11 to provide a good *in vitro* model for understanding the differentiation of human tissues (Thomson
12 and Marshall, 1998). In addition, primate ES cells provide a powerful model for understanding
13 human development and disease. Furthermore, because of the similarities between ES cells from
14 humans and primates, primate ES cells provide a good model for developing strategies to prevent
15 immune rejection of transplanted cells and for demonstrating the safety and efficacy of ES cell-
16 based therapies (Thomson, et al., 1995).

17 **Human Models [1]**

18 **Human Embryonic Stem Cell Lines Derived from Blastocysts [2]**

19 The first successful isolation of cells from the human inner cell mass of blastocysts and
20 their culture *in vitro* for at least two passages was reported by Bongso and colleagues in 1994
21 (Bongso et al., 1994). Starting with 21 spare embryos donated by 9 patients in an IVF program²,
22 this group isolated cells with typical stem cell characteristics from 17 5-day-old blastocysts
23 (approximately 100 cells) (Bongso et al., 1994). These cells were like ES cells—small and round
24 with high nuclear to cytoplasmic ratios, stained positively for alkaline phosphatase (a
25 biochemical marker for stem cells), and maintained a normal diploid karyotype—however, after
26 the second subculture, the cells differentiated into fibroblasts or died (Bongso et al., 1994).

28 In later work, Thomson and his colleagues were able to isolate human ES-like cell lines
29 and grow them continuously in culture for at least five to six months. Although these cells have

1 not passed the most stringent test—as have mouse ES cells—to determine if they can contribute
2 to the germ line, we will continue to use the term “human ES cell” throughout this report because
3 it has been widely applied by both scientists and non-scientists in reference to these cells. This
4 renewable tissue culture source of human cells, capable of differentiating into a wide variety of
5 cell types, is believed to have broad applications in basic research and transplantation therapies
6 (Gearhart 1998).

7
8 In Thomson’s work human ES cells were isolated from embryos that were originally
9 produced by *in vitro* fertilization (IVF) for clinical reproductive purposes (see Box 2-B).
10 Individuals through a careful informed consent process donated the embryos and the entire
11 protocol was reviewed and approved by an appropriately constituted Institutional Review Board
12 (Thomson et al., 1998). Thirty-six embryos were cultured for approximately five days. The inner
13 cell mass was isolated from 14 of the 20 blastocysts that developed, and 5 ES cell lines,
14 originating from 5 separate embryos, were derived (Thomson et al., 1998). The technique used to
15 derive these human ES cells was essentially the same as that used to isolate nonhuman primate
16 ES cell lines (Thomson et al., 1995).

17
18 The resulting human ES cell lines had normal karyotypes (two male and three female),
19 and were grown in culture continuously for at least five to six months (Thomson et al., 1998). In
20 addition, the cell lines expressed cell surface markers that are also found on nonhuman primate
21 ES cells (Thomson et al., 1998). Most importantly, the cell lines maintained the potential to form
22 derivatives of all three embryonic germ layers, endoderm, mesoderm, and ectoderm (Thomson et
23 al., 1998).

24
25 It is believed that research with human ES cells could offer insights into developmental
26 events that cannot be studied directly in the intact human embryo, but that have important
27 consequences in clinical areas, including birth defects, infertility, and pregnancy loss. It is also
28 speculated that the origin of many human diseases (e.g., juvenile onset diabetes) are due to events
29 that take place very early in embryonic development. Such cells will also be particularly
30 valuable for the study of the development and function of tissues that differ between mice and

humans. Importantly, these cells allow for studies that focus on understanding the differentiation of cells into specific tissues, and understanding the factors that bring about differentiation so that cells can be manipulated to generate specific cell types for therapeutic transplantation. Moreover, it may be possible to identify gene targets for new drugs, manipulate genes that could be used for tissue regeneration therapies, and understand the teratogenic or toxic effects of certain compounds (Thomson et al., 1998).

Box 2-B: *In vitro* Fertilization

The procedure of *in vitro* fertilization of human oocytes is now widely available in many countries throughout the world including the United States. It was originally developed for the treatment of infertility due to blocked fallopian tubes, but has been extended to assist patients with premature depletion of oocytes, recurrent failure of embryos to implant, and low production of functional sperm. More recently, the technique has been used in conjunction with preimplantation genetic diagnosis to enable fertile couples at risk for transmitting severe or fatal inherited diseases to have healthy children.

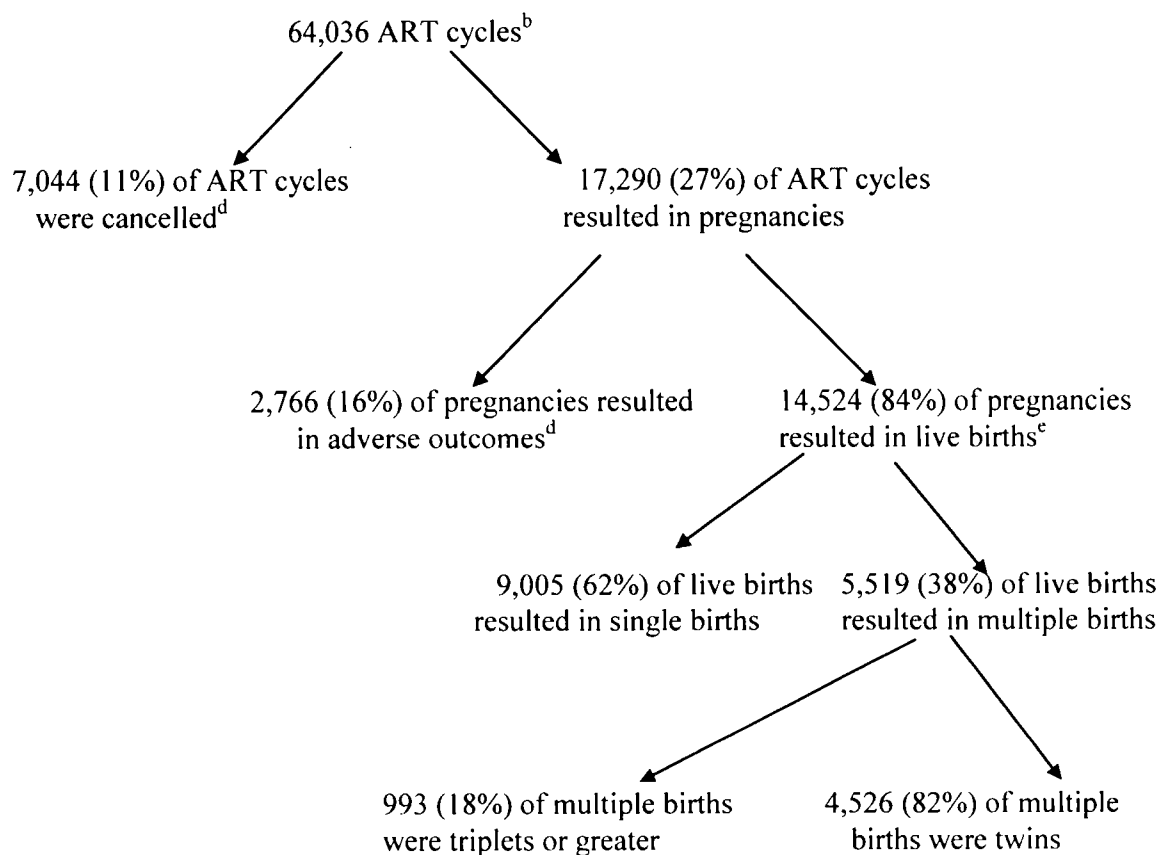
Although details of the IVF procedures vary among centers, the basic principles are as follows: oocyte donors are treated with a regimen of hormones over several days designed to stimulate the final maturation of several follicles within the ovary. This is known as hyperstimulation, and carries with it a low risk (less than 1 in 100) of an adverse reaction. Following completion of the hormone treatment mature follicles are detected by sonography and an average of around 10 are collected by transvaginal aspiration under sedation. The oocytes are then fertilized by sperm collected from a male donor and cultured in sterile fluid for about two days. When the zygote has reached the 4- to 8-cell stage, between 3 and 6 zygotes are transferred to the uterus, and untransferred embryos are usually frozen, if they are developing normally. Non-viable embryos are discarded. (See also Figure 1.) More recently, IVF specialists have begun culturing embryos to the blastocyst stage before transfer to the uterus?

The efficiency of the IVF procedure is relatively low, with approximately 5 to 10 percent of fertilized eggs giving rise to live born infants, depending on factors such as age of the recipient and the reason for infertility. In comparison, approximately 30 percent of normally conceived human

embryos result in a successful pregnancy. Embryos not transferred can be cryopreserved and stored indefinitely.

SOURCES: Report of the NIH Human Embryo Research Panel, 1994; *Assisted Reproductive Technologies: Analysis and Recommendations for Public Policy*, The New York State Task Force on Life and the Law, 1998.

Figure 2-1: 1996 Assisted Reproductive Technology Success Rates^a



^aFrom: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, and RESOLVE. 1998. 1996 Assisted Reproductive Technology Success Rates, National Summary and Fertility Clinic Reports, December 1998.

^bData are from 300 U.S. fertility clinics that provided and verified information about the outcomes of all assisted reproductive technology (ART) cycles started in their clinics in 1996.

^cFresh, nondonor cycles were canceled, most commonly because too few (egg) follicles developed. Illness unrelated to the ART procedure may also lead to cancellation. In general, cycles are canceled when chances of success are poor or risks are unacceptably high.

^dAdverse outcomes included spontaneous abortion (83%), induced abortion (10%), stillbirth (4%) or ectopic pregnancy (3%).

^eA total of 20,659 babies were born as a result of the 64,036 ART cycles carried out in 1996.

Human Embryonic Germ Cells from Fetal Primordial Germ Cells [2]

Primordial germ cells can also give rise to cells with characteristics of ES cells, and, as discussed previously, have been designated *embryonic germ (EG) cells* to distinguish their tissue of origin (Gearhart 1998). A 1998 report from John D. Gearhart of the Johns Hopkins University School of Medicine in Baltimore and his colleagues describes the establishment of human EG cell lines from human primordial germ cells (Shamblott et al., 1998). The human EG cells were isolated from the developing gonads of 5- to 9-week old fetuses that were obtained as a result of elective abortion, using an IRB-approved protocol (Shamblott et al., 1998). These human EG cell lines have morphological, immunohistochemical, and karyotypic features consistent with those of previously described ES cells and have a demonstrated ability to differentiate *in vitro* into derivatives of the three embryonic germ layers (Shamblott et al., 1998).

Fusion of Human Somatic Cells with Cow Eggs to Create Hybrid Embryonic Cells [2]

Advanced Cell Technology of Worcester, Mass. announced in a November 11, 1998 press release, that its scientists had made human somatic cells revert to the primordial state by fusing them with cow eggs to create a hybrid embryo (Wade 1998). This work with human cells was performed in 1996 by Jose Cibelli. Using 52 of his own cells, some of them white blood cells and others scraped from the inside of his cheek, Cibelli used a pulse of electricity to fuse each cell with a cow egg from which the nucleus containing the DNA had first been removed, the details of which were described in a European patent application (PCT/U397/12919, 1997). Out of these 52 attempts, only one embryo, derived from a cheek epithelial cell, developed into a blastocyst. Approximately 12 days after the fusion of cheek cell and cow egg, there were sufficient cells to allow harvesting of the inner cell mass to produce cells resembling human ES cells (PCT/U397/12919, 1997). The scientists observed that the hybrid cell quickly became more human-like as the human nucleus took control and displaced cow proteins with human proteins. However, it is difficult to judge the validity of this work and the nature of the “embryo-like” material produced since it is extremely preliminary and has not been submitted for peer review or publication in a scientific journal.

1 The stated purpose of these experiments was to create an embryo solely for the purpose of
2 establishing an ES cell line that could potentially be used to treat any disease caused by loss or
3 malfunction of cells, such as Parkinson's disease, diabetes, and heart disease. The researchers
4 emphasized that they had no intention of transferring the resulting hybrid embryos to a uterus,
5 something they considered to be unethical and unsafe (Wade 1998).

7 **Growth and Derivation of Embryonic Stem Cells [1]**

8 Human ES cells are different from many adult cells in that they have the ability to divide
9 extensively in culture. Although this property has been interpreted by non-scientists as meaning
10 that investigators can simply use existing human ES and EG cell lines to study their properties,
11 this is a misunderstanding of the science. Evidence from mouse ES cell research suggests that it
12 is essential to derive ES cells in order to further our understanding of how to differentiate these
13 cells and grow them extensively in culture.

15 There are several reasons why repeatedly deriving ES cells is necessary. First, the
16 properties of ES cells differ depending on the method used to derive them.³ Cells derived under
17 some conditions may be limited in their potential to differentiate into a particular tissue type.

19 Second, ES cells are not stable cell types that can simply be mass-produced and supplied
20 to an unlimited number of researchers. As these cells grow in culture they accumulate
21 irreversible changes, and the conditions used to grow them can influence the speed at which
22 these changes accumulate. In one careful study the ability of ES cells to generate *all* tissue in a
23 mouse was tested (Nagy et al., 1993). Typically researchers only look at the ability of ES cells to
24 contribute to some tissues. The results dramatically showed that existing cell lines commonly in
25 use by many researchers had lost the ability to generate all mouse tissues and thus to completely
26 generate live mice. When new ES cells were derived and grown for only a short time in culture,
27 they did allow all tissues to be generated. However, after about 14 doublings in culture even
28 these cells lost their ability to contribute to all tissues. The authors conclude "...[P]rolonged
29 passage in culture reduces the potential of the ES cell population as a whole. [T]he proportion of
30 cells that retain full potential diminishes with extended passage" (Nagy et al., 1993). Exactly

1 what changes occur during culture is not yet clear. The chromosome complement remains
2 normal, indicating that this criterion, although frequently used to characterize ES cells, is not a
3 very stringent assay. It could be an accumulation of mutations, changes in gene expression, or
4 epigenetic changes (Nagy et al., 1993). Thus if one scientist were to obtain cells from a
5 colleague, the properties of the cells would depend greatly on the history of how those cells were
6 grown. For this reason, many people who work with mouse ES cells re-derive the cells
7 periodically to be sure they have the potential to differentiate into or contribute to many different
8 tissues.

9
10 Finally, perhaps the most important reason for deriving ES cells rather than simply
11 working with existing cell lines is that there is a tremendous amount to be learned in the process
12 of derivation itself. It took many laboratories over 10 years to work out conditions for the
13 derivation and growth of mouse ES cells. Research on the growth and derivation of ES cells from
14 other mammalian species is only in its early stages. In fact, only mouse ES cells have the
15 property of contributing to the germline cell lineage, the most stringent criterion for ES cells.
16 Thus cells from other species are referred to as ES-like cells (Pedersen 1994). Thus further basic
17 research into the proper conditions to maintain ES cells from many species is ongoing to try to
18 understand the factors necessary to generate truly stable ES cells. Given that only two successes
19 have so far been reported on the derivation of human ES and EG cells, it is likely that significant
20 basic research into to appropriate conditions to generate stable stem cells will be necessary.

21 22 **Potential Medical Applications of Human Embryonic Stem Cell and Embryonic Germ Cell** 23 **Research [1]**

24 Although research into the use of ES and EG cells is still at an early stage, there are a
25 large number of areas in which researchers hope to make a contribution to disease treatment. The
26 ability to elucidate the mechanisms that control cell differentiation is, at the most elemental level,
27 the promise of human ES and EG cell research. This knowledge will facilitate the efficient,
28 directed differentiation of stem cells to specific cell types. The standardized production of large,
29 purified populations of, for example, human cells such as cardiomyocytes and neurons could
30 provide a substantial source of cells for drug discovery and transplantation therapies (Thomson et

al., 1998). Many diseases, such as Parkinson's disease and juvenile-onset diabetes mellitus, result from the death or dysfunction of just one or a few cell types and the replacement of those cells could offer lifelong treatment.

Substantial advances in basic cell and developmental biology are required, however, before one could direct human ES cells to lineages of human clinical importance. However, progress has already been made in the differentiation of mouse ES cells to neurons, hematopoietic cells, and cardiac muscle (Deacon 1998; Brustle 1997; Shambloott 1998). Human ES and EG cells could be put to use in targeting neurodegenerative disorders, diabetes, spinal cord injury, and hematopoietic repopulation. Current treatments for these disorders are either incomplete or create additional complications for those who suffer from them.

Use of Human Embryonic Stem Cells and Embryonic Germs Cells in Transplantation [2]

One of the major causes of organ transplantation and graft failure is immune rejection. A likely application of human ES and EG cell research is in the area of transplantation. Although much research remains to be done, ES cells derived via somatic cell nuclear transfer offer the possibility that therapies could be developed from the patient's own cells, that is, a patient's somatic cell could be fused with an enucleated ova, developed to the blastocyst stage, at which point ES cells could be derived for the development of cell-based therapy, essentially an autologous transfer. Thus, issues of tissue rejection due to foreign proteins being recognized by the immune system are entirely avoided. In addition, research to establish xenotransplantation (i.e., interspecies transplantation) as a safe and effective alternative to human organ transplantation is still in its infancy. Alternatively, other techniques could potentially be used to generate stem cells that would be immunologically compatible for transplantation purposes, such as:

- 1) banking of multiple cell lines representing a spectrum of major histocompatibility complex (MHC) alleles to serve as a source for MHC matching; and/or
- 2) creation of universal donor lines, in which the MHC genes could be genetically altered so rejection would not occur, an approach that has been tried with moderate success in the mouse (NIH 1999).

Autologous transplants would obviate the need for immunosuppressive agents in transplantation and the ensuing susceptibility to other diseases. In addition to eliminating the need for immunosuppressive drugs, this would address problems ranging from the supply of donor organs to the difficulty of finding matches between donors and recipients. Research on ES cells could lead to cures for diseases that require treatment through transplantation, including autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and type-I diabetes (Varmus 1998; Juvenile Diabetes Foundation 1998). Treatment of type-I diabetes would involve the transplantation of pancreatic islet cells or beta cells produced from autologous embryonic stem cells. These cells would enter the pancreas and provide normal insulin production by replacing the failing resident islet cells.

Studies of Human Reproduction and Developmental Biology [2]

Research using human ES and EG cells could offer insights into developmental events that cannot be studied directly in the intact human embryo but that have important consequences in clinical areas, including birth defects, infertility, and pregnancy loss (Thomson et al., 1998). ES and EG cells provide large quantities of homogeneous material that can be used for biochemical analysis of the patterns of gene expression and the molecular mechanisms of embryonic differentiation.

Cancer Therapy [2]

Human ES and EG cells may be used to reduce the tissue toxicity brought on by cancer therapy (NCI 1999). Already bone marrow stem cells, representing a more committed stem cell, are used to treat patients after high-dose chemotherapy. However, the recovered blood cells appear limited in their ability to recognize abnormal cells such as cancer cells. It is possible that injections of ES and EG cells would revive the complete immune response to patients undergoing bone marrow transplantation. Current approaches aimed at manipulating the immune system after high dose chemotherapy, so that it specifically recognizes cancer cells, have not yet succeeded.

Diseases of the Nervous System [2]

Some believe that in no area of medicine are the potential benefits of ES and EG cell research greater than in diseases of the nervous system (Senate testimonies, Gearhart, Varmus). The most obvious reason is that so many of these diseases result from the loss of nerve cells, and mature nerve cells cannot divide to replace those that are lost. For example, in Parkinson's disease, nerve cells that make the chemical dopamine die; in Alzheimer's disease, it is the cells that make acetylcholine that die; in Huntington's disease the cells that make GABA die, in multiple sclerosis, cells that make myelin die; in amyotrophic lateral sclerosis the motor nerve cells that activate muscles die. In stroke, brain trauma, spinal cord injury, and the many causes of cerebral palsy and mental retardation, numerous types of cells are lost with no built-in mechanism for replacing them.

Preliminary results from fetal tissue transplantation trials for Parkinson's disease suggest that supplying new cells to a structure as intricate as the brain can slow or stop disease progression (Freed 1999). Yet the difficulty of obtaining enough cells of the right type, that is, dopamine producing nerve cells—limits the application of this therapy. In 1999, scientists developed methods in animal models to isolate dopamine precursor cells from the dopamine – producing region of the brain and coax them to proliferate for several generations in cell culture. When these cells were implanted into the brains of rodents with experimental Parkinson's disease, the animals showed improvements in their movement control (NINDS 1999). Scientists have also learned to instruct a stem cell from even a non-dopamine region to make dopamine (Wagner, et al., 1999). A large supply of “dopamine competent” stem cells, such as ES cell lines, could remove the barrier of limited amounts of tissue. (See Box 2-C). Other diseases that might benefit from a similar approach are spinal cord injury, epilepsy, multiple sclerosis, stroke, and pediatric causes of cerebral palsy and mental retardation. In mice, neural stem cells have already been shown to be effective in replacing cells and genes throughout the brain, at multiple ages (Snyder, Taylor, and Woolfe 1995; Snyder et al., 1997; Rosario et al., 1997; Yandava, Billingham, and Snyder, 1999; Lacorazza et al., 1996). Engraftable human neural stem cells have also recently been isolated (Flax et al., 1998).

Box 3-C: Potential Treatment for Parkinson's Disease

Parkinson's disease is a degenerative brain disease that affects 2 percent of the population over age 70. Symptoms include slow and stiff movements, problems with balance and walking, and tremor. In more advanced cases, the patient has a fixed, staring expression, walks with a stooped posture and short, shuffling pace, and has difficulty initiating voluntary movements. Falls, difficulty swallowing, incontinence, and dementia may occur in the late stages. Patients often lose the ability to care for themselves and may become bedridden.

The cause of this illness is a deficiency of the neurotransmitter dopamine in specific areas of the brain. Treatment with drugs such as levodopa often is very effective in relieving the symptoms. However, as the disease progresses, treatment often becomes more problematic, with irregular responses, difficulty adjusting doses, and the development of side effects such as involuntary writhing movements. Brain surgery with transplantation of human fetal tissue has shown promise as therapy.

Stem cell transplantation may also be a promising therapy for Parkinson's. Injection of stem cells that can differentiate into brain cells may offer a means of replenishing neurons capable of synthesizing the deficient neurotransmitter, dopamine. It is possible that stem cell transplantation may be simpler and more readily available than fetal tissue transplantation.

Diseases of the Bone and Cartilage [2]

Because ES and EG cells constitute a relatively self-renewing population of cells, they can be cultured to generate greater numbers of bone or cartilage cells than could be obtained from a tissue sample. If a self-renewing, but controlled, population of stem cells can be established in a transplant recipient, it could effect long-term correction of many diseases and degenerative conditions in which bone or cartilage cells are deficient in numbers or defective in function. This could be done either by transplanting ES and EG cells to a recipient, or by genetically modifying a person's own stem cells and returning them to the marrow. Such an approach holds promise for the treatment of genetic disorders of bone and cartilage, such as osteogenesis imperfecta and the various chondrodysplasias. In a somewhat different potential

1 application, stem cells could perhaps be stimulated in culture to develop into either bone or
2 cartilage-producing cells. These cells could then be introduced into the damaged areas of joint
3 cartilage in cases of osteoarthritis, or into large gaps in bone that can arise from fractures or
4 surgery. This sort of repair would have a number of advantages over the current practice of tissue
5 grafting (NIAMS 1999).

7 **Blood Disorders [2]**

8 The globin proteins are essential for transport of oxygen in the blood. Different globins
9 are expressed at different developmental stages. The epsilon globin gene is expressed only in
10 embryonic red blood cells. When this gene—which is not normally expressed in the adult—is
11 artificially turned on in sickle cell patients, it blocks the sickling of the cells that contain sickle
12 cell hemoglobin. Research involving ES cells could help answer questions about how to turn on
13 the epsilon globin gene in adult blood cells and thereby halt the disease process. Stem cell
14 research may also help produce transplantable cells that would not contain the sickle cell
15 mutation.

17 **Toxicity and Drug Testing [2]**

18 Human stem cell research offers promise for use in testing the beneficial and toxic effects
19 of biologicals, chemicals and drugs in the most relevant species for clinical validity, humans.
20 Such studies could lead to fewer, less costly, better designed human clinical trials yielding more
21 specific diagnostic procedures and more effective systemic therapies. Beyond the drug
22 development screening of pharmacological agents for toxicity and/or efficacy, human stem cell
23 research could define new research approaches for clarifying the complex association of
24 environmental agents with human disease processes (NIEHS 1999). It also makes possible a new
25 means of conducting detailed investigations of the underlying mechanisms of the effects of
26 environmental toxins or mixtures of toxins, including their subtle effects on the developing
27 embryonic and fetal development tissue systems.

29 **Transplantable Organs [2]**

30 Several researchers are investigating ways to isolate adult stem cells and create

transplantable organs that may be used to treat a multitude of diseases that do not rely on the use of embryonic or fetal tissue. Moreover, if it is found to be possible to differentiate embryonic stem cells into specific cell types, such stem cells could be an important source of cells for organ growth. For example, recent developments in animals have shown that it may be possible to create entire transplantable organs from a tissue base in a manner that would overcome such problems as the limited supply of organs and tissue rejection. If such a tissue base could be produced by directing the growth of human embryonic cells, this has the potential to be a major breakthrough.

For example, using tissue engineering methods, researchers have successfully grown bladders in the laboratory, implanted them into dogs, and shown them to be functional (Oberpenning et al., 1999). To create the bladders, small biopsies of tissue were taken from dog bladders which were teased apart to isolate the urothelial tissue and muscle tissue which were then grown separately in culture (Tanne 1999). The tissue was then applied to a mold of biodegradable material with the urothelial tissue on the inside and the muscle tissue on the outside. The new organs were transplanted within five weeks (Tanne 1999).

Dogs that received the tissue-engineered organs regained 95 percent of their original bladder capacity, were continent, and voided normally. When the new organs were examined 11 months later, they were completely covered with urothelial and muscle tissue, and had both nerve and blood vessel growth. Dogs who did not undergo reconstructive procedures or only received implants of the biodegradable molds did not regain normal bladder function (Oberpenning et al., 1999).

This accomplishment marks the first time a mammalian organ has been grown in a laboratory. The ability to create new organs by seeding molds with cells of specific tissue types would be extremely useful to treat babies with congenital malformations of organs and people who have lost organs due to trauma or disease (Tanne 1999).

Summary [1]

Currently, human ES cells can be derived from the inner cell mass of a blastocyst (those

1 cells within the conceptus that form the embryo proper) and EG cells from primordial germ cells
2 of fetuses. These cells, present in the very early stages of embryo and fetal development, can
3 generate all of the human cell types and are capable, at least for some time, of self-renewal. A
4 relatively renewable tissue culture source of human cells capable of being used to generate a
5 wide variety of cell types would have broad applications in basic research, transplantation, and
6 other important therapies. A major step in realizing this goal was taken in 1998 with the
7 demonstration that human ES and EG cells can be grown in culture. The clinical potential for
8 these stem cells is vast. Such cells will be important for in vitro studies of normal human
9 embryogenesis, abnormal development, human gene discovery, and drug and teratogen testing
10 and as a renewable source of cells for tissue transplantation, cell replacement, and gene therapies.
11

¹ Thompson, J.A. Public testimony before NBAC. January 19, 1999. Washington, D.C.

² Consent to carry out this study was approved by the hospital ethical committee based on the guidelines on Assisted Reproductive Technology of the Ministry of Health, Singapore that experimentation of human embryos up to day 14 of embryonic growth may be allowed (Bongso et al., 1994).

³ Hogan, B. NBAC Meeting. February 3, 1999. Princeton, N.J.

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alex

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> Attached for your review is the next version of chapter 1 of the stem
cell
> report. We will be sending chapters out as they become available. Please
try to
> get your responses and comments back on this chapter by Monday, August
2. As
> always, please call if you would like a fax or hard copy version. The
person to
> call is Kerry Jo Lee at 301-402-4242.
>
> Thanks,
>
> Kathi
>
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CHAPTER 2: HUMAN STEM CELL RESEARCH AND THE POTENTIAL FOR CLINICAL APPLICATION

Introduction [1]

The stem cell is a unique and essential cell type found in animals. Many kinds of stem cells are found in the body, with some more differentiated, or committed, to a particular function than others. In other words, when stem cells divide, some of the progeny mature into cells of a specific type (heart, muscle, blood, or brain cells), while others remain stem cells, ready to repair some of the everyday wear and tear undergone by our bodies. These stem cells are capable of continually reproducing themselves and serve to renew tissue throughout an individual's life. For example, they continually regenerate the lining of the gut, revitalize skin, and produce a whole range of blood cells. Although the term "stem cell" commonly is used to refer to the cells within the adult organism that renew tissue (e.g., hematopoietic stem cells, a type of cell found in the blood), the most fundamental and extraordinary of the stem cells are found in the early-stage embryo (Van Blerkom 1994). These *embryonic stem* (ES) cells, unlike the more differentiated adult stem cells or other cell types, retain the special ability to develop into nearly any cell type. *Embryonic germ* (EG) cells, which originate from the primordial reproductive cells of the developing fetus, have properties similar to ES cells.

Because stem cells have the ability to proliferate and renew themselves over the lifetime of the organism—while retaining all of their multilineage potential—scientists have long recognized the potential of using such cells to generate a large number of specialized cells or tissue through amplification, a possibility that could allow the generation of new cells for the treatment of injury or disease. If, therefore, it was possible to control the differentiation of human ES cells in culture, the resulting cells could be used clinically to potentially help repair damage caused by such diseases as heart failure, diabetes, and certain neurodegenerative diseases.

In late 1998 three separate reports brought to the forefront the scientific and clinical prospects of human stem cell research. The first two reports, published by two independent teams

1 of scientists, describe the first successful isolation and culture in the laboratory of human ES and
2 EG cells. The research of both teams was supported by private funds from Geron Corp., a
3 biotechnology company in Menlo Park, CA. Dr. John Gearhart and his colleagues derived human
4 EG cells from primordial gonadal tissue, which was obtained from fetal tissue following elective
5 abortion (Shamblott et al., 1998). Dr. James Thomson and his co-workers derived human ES
6 cells from the blastocyst stage of early embryos donated by couples that had undergone infertility
7 treatment (Thomson and Marshall 1998). The ES and EG cells derived by each of these means
8 appear to be similar in structure, function, and potential, but it will take more research to fully
9 verify this claim (Varmus 1998). In addition, on November 12, 1998, the *New York Times*
10 reported that Advanced Cell Technology of Worcester, Massachusetts had carried out related
11 research, although the work has not yet been peer- reviewed, published, or verified. In this
12 report, the company claims to have made human cells revert to the primordial state by fusing
13 them with cow eggs, creating a hybrid embryo from which a small clump of cells resembling
14 human ES cells appear to have been isolated (Wade 1998).

15
16 The methodologies used by these investigators for deriving human ES and EG cells are
17 based on techniques used in mice since the early 1980s and, more recently, from non-human
18 primates and other animals. The isolation and culturing of these cells, however, open certain
19 avenues of important research and future clinical possibilities for the first time. At the most basic
20 level, the isolation of these cells allows scientists to focus on how ES and EG cells differentiate
21 into specific types of cells, with the goal of identifying the genetic and environmental signals that
22 direct their specialization into specific cell types. Such studies are ongoing using mouse stem
23 cells, but comparable studies with human cells will be needed to determine whether or not the
24 signals are the same. This research might, for example, lead to the discovery of new ways to treat
25 a variety of diseases including degenerative diseases, birth defects and cancer. This research
26 would build on investigations conducted over the last decade, in which laboratory animals have
27 been used to determine whether ES cells can be used to re-establish tissue in an adult organism
28 (Hall and Watt 1989; Corn et al., 1991; Hollands 1991; Diukman and Golbus 1992). Through
29 processes scientists are only beginning to understand, these primitive stem cells can be
30 stimulated to specialize so that they become precursors to different cell types, which may then be

used medically for replacement of tissues such as muscle, skin, nerve, or liver.

Box 2-A: Early Development of the Human Embryo

In humans, fertilization occurs in the fallopian tube. Fertilization, the union of an oocyte (egg) and sperm, results in the formation of the zygote. It takes 3-4 days for the zygote to travel down the fallopian tube to the uterus. As the zygote travels through the fallopian tube, several cell divisions (cleavages) occur.

The first division occurs about 36 hours after fertilization, when the zygote begins to cleave into two cells called blastomeres. At about 60 hours after fertilization, the 2 blastomeres divide again to form 4 blastomeres. At 3 days post fertilization, the 4 blastomeres divide to form 8 cells. Each blastomere becomes smaller with each subsequent division. In this early stage of development, all of the blastomeres are of equal size. These cells are unspecialized and have the capacity to differentiate into any of the cell types of the embryo as well as the essential membranes and tissue that will support the development of the embryo. Therefore, one or more of the blastomeres can be removed without affecting the ability of the other blastomeres to develop into a fetus. In fact, if an embryo separates in half at this early stage of development, identical twins—two genetically identical individuals—develop.

When the cell division reaches about 16 cells, the zygote is called a morula. It leaves the fallopian tube and enters the uterine cavity 3 to 4 days after fertilization. After reaching the uterus, the developing zygote usually remains in the uterine cavity an additional 4 to 5 days before it implants in the endometrium (uterine wall), which means that implantation ordinarily occurs on the 7th or 8th day following fertilization.

Cell division continues, creating a cavity known as a blastocoele in the center of the morula. With the appearance of the cavity in the center, the entire structure is now called a blastocyst. This first specialization event occurs just before the zygote attaches to the uterus, around 6 to 7 days after fertilization, when there are approximately 100 cells. This specialization involves the formation of an outer layer of trophoblast cells, which will give rise to part of the placenta, surrounding a group of about 20 to 30 inner cells (the inner cell mass or ICM) that remain undifferentiated. At this stage, these cells can no longer give rise to all of the cells necessary to form an entire organism, and therefore are not capable of developing into an entire

human being. In general, as cells further differentiate they lose the capacity to enter developmental pathways previously open to them.

As the blastocyst attaches to the uterus, the outer layer of cells secretes an enzyme, which erodes the epithelial uterine lining and creates an implantation site for the blastocyst. Once implantation has taken place, the zygote becomes an embryo. The trophoblast and sub-lying cells proliferate rapidly to form the placenta and the various membranes that surround and nourish the developing embryonic cells.

In the week following implantation, the inner cells of the blastocyst give rise to more of the placental tissue and eventually to a small disc of cells from which the fetus will develop. By 14 days the embryonic disc is about 0.5 mm in diameter and consists of about 2,000 cells. It is at this time that the first stage of organized development, known as gastrulation, is initiated, leading over the next few days to the first appearance of differentiated tissues of the body, including primitive neural cells. Gastrulation is the process by which the bilaminar (two-layered) embryonic disc is converted into a trilaminar (three-layered) embryonic disc and its onset at day 14 *in vivo* is marked by the appearance of the primitive streak. This is a region in which cells move from one layer to another in an organized way.

During the third week, the embryo grows to 2.3 mm long, and the precursors of most of the major organ systems begin to form. At the beginning of the third month the embryo becomes a fetus. During the 3rd to 9th month, the organ systems and tissues of the fetus continue to develop.

Stem Cell Types [1]

Scientists often distinguish between different kinds of stem cells depending on their origin and their potential to differentiate. Cells derived from malignant embryonic tumors, or teratocarcinomas, are called **embryonal carcinoma cells (EC cells)**, cells derived from the inner cell mass of a blastocyst embryo are called **embryonic stem cells (ES cells)**, and cells that are derived from precursors of germ cells from a fetus are called **embryonic germ cells (EG cells)**. In addition, stem cells can be found in the adult organism, for example, in bone marrow; they may possibly also be found in skin and intestine. These **adult stem (AS) cells** serve to replenish tissues where cells often have limited life span, such as the skin, intestine and blood. While there

1 is exciting new data that suggests that stem cells found in the adult organism are not restricted to
2 produce only cells from the tissue in which they reside (Bjornson et al., 1999), it is unlikely that
3 these cells are capable of differentiating into all cell types. In contrast, because human ES and
4 EG cells are believed to be capable of differentiating into all cell types they are likely to be of
5 clinical use in treating a variety of diseases, especially those for which organ-specific stem cells
6 are difficult to isolate and/or use.

7 **Embryonic Germ Cells [2]**

8 Primordial germ cells are the embryonic precursors of the sperm and ova of the adult
9 animal (Donovan 1998). The establishment of the germ line in the embryo involves the
10 separation of primordial germ cells from the somatic cells, proliferation of primordial germ cells,
11 migration of these cells to the gonad, and finally their differentiation to gametes (Donovan 1994).
12 Primordial germ cells are the only cells in the body that can give rise to successive generations,
13 while the somatic cells that form the body of the animal are destined for death once they start to
14 differentiate (Matsui 1998).

15
16 In culture, primordial germ cells can give rise to stem cells called embryonic germ (EG)
17 cells that are capable of differentiating into cells of multiple lineages (Donovan 1998). In the
18 body, primordial germ cells normally give rise to gametes, but sometimes if the developmental
19 process goes awry, they become embryonal carcinoma cells. Such cells are the stem cells of
20 teratomas, which are tumors containing derivatives of the three primary germ layers (Donovan
21 1998).

22
23 EG cells form embryoid bodies in culture, give rise to teratomas when introduced into
24 histocompatible animals, and form germline chimeras when introduced into a host blastocyst
25 (Donovan 1998). The derivation of EG cells directly from primordial germ cells represents a
26 mechanism to study some aspects of primordial germ cell development such as imprinting and
27 differentiation (Donovan 1994). At the same time it may be difficult to get an adequate supply of
28 fetal tissue with the appropriate properties to provide the relevant cell lines needed for both
29 research and clinical needs.

Embryonic Stem Cells [2]

In mammalian embryonic development, cell division gives rise to differentiated daughter cells that eventually comprise the mature animal. As cells become committed to a particular lineage, or cell type, a progressive decrease in developmental potential presumably occurs. Early in embryonic development (until about 16 cells), each cell of the early cleavage-stage embryo has the developmental potential to contribute to any embryonic or extraembryonic cell type (Winkel and Pedersen 1988). However, by the blastocyst stage, cells of the trophectoderm are irreversibly committed to forming the placenta and other trophectoderm lineages (Winkel and Pedersen 1988). By six to seven days post fertilization, the inner cell mass has divided to form two layers, which give rise to the embryo proper, and extra-embryonic tissues (Gardner 1982).

Although the cells of the inner cell mass are precursors to all adult tissues, they can only proliferate and replace themselves in the intact embryo for a limited time before they become committed to specific lineages (Thomson and Marshall 1998). ES cells are derived from cells of the inner cell mass. Once they are placed in the appropriate culture (laboratory growth) conditions, these cells seem to be capable of extensive, undifferentiated proliferation *in vitro*, and maintain the potential to contribute to all adult cell types (Evans and Kaufman 1981; Martin 1981).

While these embryonic cells are “stem cells,” they differ substantially from the stem cells found within the fully developed, or adult organism (see below). Most importantly, ES cells are highly proliferative, both in the embryo as well as in culture, while some stem cells of the adult can be almost totally quiescent, and may be more difficult to maintain and expand in culture (Van Blerkom 1994). Therefore, it appears that if stem cells were someday to be used for the treatment of disease, it might be advantageous to use ES cells for some disorders.

Sources of Human Embryonic Stem Cells [3]

ES cells are derived from early embryos in culture. Because of moral concerns, including respect for human dignity, this report distinguishes between three sources of ES cells: 1) embryos created by *in vitro* fertilization for infertility treatments that were not implanted because they

1 were no longer needed by the couple; 2) embryos created expressly for research by *in vitro*
2 fertilization; and 3) embryos resulting from somatic cell nuclear transfer (SCNT), or other
3 cloning techniques. SCNT has opened the possibility of an alternative way to create ES cells. If
4 the nucleus is removed from an immature egg (oocyte) and a mature diploid nucleus is inserted,
5 the resulting cell will divide and develop with many characteristics of an embryo. In animal
6 experiments when an SCNT-derived embryo is transferred to a surrogate mother, a successful
7 pregnancy can be established. This was the technique used to generate the now famous cloned
8 sheep Dolly. If instead of being transferred to a surrogate, the SCNT-derived embryo is kept in
9 culture, is allowed to divide, and is then dissociated, ES cells can be derived. The potential
10 advantage of using SCNT technology to create ES cells is that a somatic cell from an individual
11 can be used to create ES cells that are completely compatible with that individual's tissue type. If
12 cells or tissues are generated from these ES cells for transplant into a person, this tissue type
13 compatibility may avoid many of the problems associated with tissue graft rejection currently
14 encountered in clinical treatment of a variety of diseases.

15
16 The use of SCNT into an oocyte has been criticized as an asexual or "unnatural" way of
17 creating a human embryo. However, it is important to distinguish the technique of SCNT from
18 the type of cell that is created, that is, SCNT techniques might also be used with recipient cells
19 other than oocytes. For example, ES cells with matched tissue types for transplant might be
20 generated by SCNT into an enucleated ES cell.¹ This possibility has not yet been explored
21 experimentally, but it may be less morally problematic to many as the cell created would not be
22 an embryo with the potential to continue development.

23 **Stem Cells Found in the Postnatal and Adult Organism [2]**

24 In the adult mammal, cell division occurs in order to maintain a constant number of
25 terminally differentiated cells in tissues where cells are lost due to injury, disease, or natural cell
26 death. Cells with a high turnover rate are replaced through a highly regulated process of
27 proliferation, differentiation, and apoptosis (programmed cell death) from relatively
28 undifferentiated stem cells, or precursor cells (Thomson and Marshall 1998). The best known
29 example of an adult stem cell is the hematopoietic stem cell found in bone marrow, which is

1 responsible for the production of all types of blood cells (Iscove 1990). Other examples of stem
2 cells include the skin epithelium and the epithelium of the small intestine (Hall and Watt 1989).
3 In the human small intestine, for example, approximately 10^{11} (100 billion) cells are shed and
4 must be replaced daily (Potten and Loeffler 1990). These tissues contain subpopulations of
5 dividing stem cells that generate replacements for the relatively short-lived, terminally
6 differentiated cells. Much of the debate in the stem cell field revolves around determining the
7 breadth of the potential of these cells; can they give rise to all cell types of that organ or only a
8 restricted few?

9
10 The successful cloning of Dolly the sheep demonstrated that even somatic cells are
11 capable of forming every cell of an organism after nuclear transfer into an oocyte (Wilmut, et al.,
12 1997). Preliminary studies of stem cells obtained from various systems of the adult organism
13 suggest that in some cases the reactivation of dormant genetic programs may not require nuclear
14 transfer or experimental modification of the genome. Although research in this area is
15 preliminary, this particular class of stem cells, i.e. adult stem cells, might be able to differentiate
16 along several, but probably not all, cell lineages in response to an appropriate pattern of
17 stimulation.

18 **Neural Stem Cells [3]**

19 It has been recognized for a number of years that transplantation of fresh fetal tissue into
20 the diseased adult brain may be a promising therapy for neurodegenerative disorders, and has
21 recently been shown to be effective in younger patients with Parkinson's disease (reported by
22 Curt Freed to American Academy of Neurology, April 21, 1999). This technique has several
23 disadvantages, however, such as the necessity of timing the surgery to the availability of large
24 amounts of fresh fetal tissue, the need to quickly screen for infectious diseases, and the limited
25 amount of donor fetal tissue available (Bjorkund 1993; Cattaneo and McKay 1991). By
26 developing techniques to culture and expand primary fetal neural cells before transplantation,
27 some of the problems of using fresh tissue may be eliminated. In addition, it may be possible to
28 direct cultured cells to develop along certain lineages or to express specific genes before they are

1 transplanted, so that, for example, dopamine-producing cells could be selectively grown to treat
2 Parkinson's disease (Cattaneo and McKay 1991; Snyder 1994).

3
4 Indeed, it has already been demonstrated that neural stem cells are capable of gene
5 (Snyder et al., 1995) and cellular (Snyder et al., 1997; Rosario et al., 1997; Yandava,
6 Billingham, and Snyder 1999) replacement in models of neural disease. Interestingly, in many of
7 these experiments one stable clone of mouse neural stem cells could be used from individual to
8 individual, strain to strain, and disease to disease, regardless of recipient age within the species,
9 without immunorejection or the need for immunosuppression, suggesting that unique immune
10 qualities may exist within stem cells, which might allow them to be “universal donors.”
11 Moreover, the possibility exists that a good deal of instructive cues for differentiation may
12 actually come from interaction with damaged CNS tissue itself.

13
14 The embryonic nervous system arises from the ectoderm. The first cell type to
15 differentiate from the uncommitted precursor cells is the neuron, followed by the
16 oligodendrocyte, and then the astrocyte (Frederiksen and McKay 1988). Recently, Angelo
17 Vescovi, a neurobiologist at the National Neurological Institute Carlo Besta in Milan, Italy, and
18 his colleagues reported that neural stem cells, which give rise to the three main types of brain
19 cells, can also become blood cells when transplanted into mice whose own blood-forming tissue,
20 the bone marrow, has been mostly destroyed (Bjornson et al., 1999). The study did not explain
21 what caused the neural cells to turn into blood cells, but the investigators speculate that the
22 neural cells might be responding to the same signals that normally stimulate the few remaining
23 blood stem cells to reproduce and mature after irradiation wipes out most of the bone marrow
24 (Strauss 1999). Although this research is preliminary and has not yet been conducted using
25 human cells, it opens the possibility of using neural stem cell transplants to treat human blood
26 cell disorders such as aplastic anemia and severe combined immunodeficiency—an appealing
27 idea, as bone marrow stem cells do not replenish themselves well in laboratory cultures.
28 However, the problem of access to such cells in humans remains, as such cells have to be
29 obtained from the brain, an invasive and risky procedure. This research also opens up the
30 possibility that other apparently restricted adult stem cells may retain the ability to differentiate

1 into several different types of cells if exposed to the right external environment. However,
2 further research is required in this area.

4 **Mesenchymal Stem Cells [3]**

5 Human mesenchymal stem cells, which are present in adult bone marrow, can replicate as
6 undifferentiated cells and have the potential to differentiate to lineages of mesenchymal tissues,
7 including bone, cartilage, fat, tendon, muscle, and marrow stroma (Pittenger et al., 1999). In a
8 recent experiment, cells that have the characteristics of human mesenchymal stem cells were
9 isolated from marrow aspirates of volunteer donors. Individual stem cells were identified that,
10 when expanded to colonies, retained their multilineage potential. This shows that isolated
11 expanded human mesenchymal stem cells in culture will differentiate, in a controlled manner, to
12 multiple—but limited—lineages. It is speculated that these particular adult stem cells could be
13 induced to differentiate exclusively into the adipocytic, chondrocytic, or osteocytic lineages,
14 which might be used to treat various bone diseases.

16 The specific environmental cues to initiate the proliferation and differentiation of these
17 cells are not understood (Pittenger et al., 1999). The ability to isolate, expand, and direct the
18 differentiation of such cells in culture to particular lineages, however, provides the opportunity to
19 study events associated with cell commitment and differentiation. The human mesenchymal stem
20 cells isolated by Pittenger and colleagues appear to have the ability to proliferate extensively, and
21 maintain the ability to differentiate into certain cell types in culture. Their cultivation and
22 selective differentiation should provide further understanding of this important progenitor of
23 multiple tissue types and the potential of new therapeutic approaches for the restoration of
24 damaged or diseased tissue (Pittenger et al., 1999).

25 **Animal Models [1]**

26 ES cells were first derived from mouse embryos, and have become the principal model
27 system for the study of these cells (Evans and Kaufman 1981; Martin 1981). More recently, cells
28 with some properties of ES cells have been derived from cows, pigs, rats, sheep, hamsters,
29 rabbits and primates (reviewed in Pedersen, 1994; see Table 2-1). However only in cows, pigs

and rats did these ES cells contribute to a chimeric animal and in none of these was there germline contribution of the ES cell lineage (ref?). This germ line contribution is the most stringent criterion for ES cells.

Table 2-1. Stem Cells Isolated from Mammals

Species	References
Mouse	Evans and Kaufman, 1981 Martin, 1981
Rat	Iannaccone et al., 1994
Hamster	Doetschman, Williams, and Maeda 1988
Mink	Sukoyan et al., 1992 Sukoyan et al., 1993
Rabbit	Cole et al., 1965a, b Moreadith and Graves, 1992 Giles et al., 1993 Graves and Moreadith, 1993
Sheep	Handyside et al., 1987 Piedrahita, Anderson, and Bondurant 1990 Notarianni et al., 1990
Pig	Piedrahita et al., 1988 Evans et al., 1990 Notarianni et al., 1990 Piedrahita et al., 1990 Hochereau-de Reiviers and Perreau, 1993 Talbot et al., 1993 Wheeler 1994 Shim et al., 1997
Cow	Evans et al., 1990 Saito, Strelchenko, and Niemann, 1992 Strelchenko and Stice, 1994 Cibelli et al., 1998
Common Marmoset	Thomson et al., 1996
Rhesus Monkey	Thomson et al., 1995
Human	Bongso et al., 1994 Shamblott et al., 1988 Thomson et al., 1998

Mouse Embryonic Stem Cells [2]

ES cells were first isolated from mouse blastocysts in 1981 (Evans and Kaufman 1981;

1 Martin 1981). Blastocysts were placed in culture and allowed to attach to the culture dish so that
2 trophoblast cells spread out, while the undifferentiated inner cells (the inner cell mass) continued
3 to grow as a tight, but unorganized, cluster. Before the inner cell mass developed into the
4 equivalent of the embryonic disc, it was drawn up into a fine pipette, dissociated into single cells,
5 and dispersed into another dish with a rich culture medium. Under these circumstances, the
6 dissociated cells continued to grow rapidly for an extended period of time.

7
8 Mouse ES cells cannot become organized into an embryo by themselves or implant into
9 the uterus if placed there. However, if the cells are injected back into a new blastocyst, they can
10 intermingle with the host inner cell mass to make a chimera and take part in normal
11 development, eventually contributing to all the tissues of the adult mouse, including nerve,
12 blood, skin, bone, and germ cells (reviewed in Robertson and Bradley, 1986). This indicates that
13 mouse ES cells have not lost the capacity to give rise to specialized tissues, but they will not do
14 so unless placed in the right environment.

15
16 The ability of mouse ES cells to enter the germ line in chimeras allows the introduction of
17 specific genetic changes into the mouse genome and offers a direct approach to understanding
18 gene function in the intact animal (Rossant, Bernelot-Moens, and Nagy, 1993). Using the
19 technique of homologous recombination in which a gene is either modified or disabled
20 (“knocked out”), mouse ES cells can be derived that contain specific gene alterations. These
21 genetically altered cells can then be used to form chimeras with normal embryos and
22 subsequently bred to generate a mouse lacking one specific gene or containing an extra or altered
23 gene.

24
25 Mouse ES cells have also been extremely useful as models of the early differentiation
26 events that take place during the development of mammalian embryos (reviewed in Pedersen,
27 1994). For example:

- 28 • When mouse ES cells were allowed to differentiate in culture, beating heart cells formed
29 spontaneously, providing a model for cardiac-specific gene expression, and the development
30 of cardiac muscle and blood vessels (Robbins et al., 1990; Wobus, Halukat, and Heschler,

1991; Chen and Kosco, 1993; Doetschman et al., 1993; Miller-Hance et al., 1993; Muthuchamy et al., 1993).

- Blood formation will occur spontaneously in ES cell-derived embryoid bodies, and can be augmented by modifying the culture conditions (reviewed in Snodgrass, Schmitt, and Bruyns 1992). Therefore, hematopoietic stem cells have been studied extensively to determine the conditions for differentiation, survival, and proliferation of blood cells.
- Several studies have highlighted the importance of growth and differentiation factors in the regulation of mammalian development. For example, the maintenance of mouse ES cells in an undifferentiated state was found to require the presence of leukemia inhibitory factor (LIF), a differentiation-inhibiting factor (reviewed in Fry, 1992). Other studies have found several growth and differentiation factors to be important in ES cell development and differentiation, including activins, colony-stimulating factor, erythropoietin, basic fibroblast growth factor, insulin-like growth factor 2, interleukins, parathyroid hormone-related peptide, platelet-derived growth factor, steel factor, and transforming growth factor β (reviewed in Pedersen, 1994).
- In mid-gestation embryos and the adult mouse, only one parental allele of imprinted genes is expressed. However, studies have suggested that there is limited relaxation of imprinting in ES cells so that both maternal and paternal alleles are expressed (reviewed in Pedersen, 1994).

By understanding the mechanisms responsible for growth and differentiation in embryonic development, it may then be possible to attempt to regulate the differentiation of ES cells along specific pathways. The knowledge gained from these types of studies could someday lead to the effective treatment of certain important human diseases.

Historically, because of its well-defined genetics, short gestational times, ease of cultivation, and large litters, the mouse has been one of the primary models for the study of mammalian embryonic development. However, there are several differences between early mouse development and early human development, including differences in:

- the timing of embryonic genome expression (Braude, Bolton, and Moore 1988);

- the formation, structure, and function of the fetal membranes and placenta (Luckett 1975, 1978; Benirschke and Kaufmann 1990); and
- formation of an egg cylinder in the mouse as opposed to an embryonic disc in humans (O'Rahilly and Muller 1987; Kaufmann 1992).

Therefore, other animal models as well as new models that would directly allow the study of human embryonic development are crucial for our comprehension of early human development and for understanding the growth requirements of human stem cells of specific lineages.

Bovine Embryonic Stem Cells [2]

The first bovine ES-like cells were reported by Saito et al. (Saito, Strelchenko, and Niemann 1992). More recently, transgenic bovine ES-like cells were derived by using nuclear transfer of fetal fibroblasts to enucleated bovine oocytes (Cibelli et al., 1998). This technique involved introducing a marker gene into bovine fibroblasts from a 55-day old fetus and then fusing the transgenic fibroblasts to enucleated oocytes to produce blastocyst-stage nuclear transplant embryos (Cibelli et al., 1998). ES-like cells were then derived from these embryos and used to create chimeric embryos. When reintroduced into preimplantation embryos, these transgenic ES-like cells differentiated into derivatives from the three embryonic germ layers, ectoderm, mesoderm, and endoderm (Cibelli et al., 1998). Bovine ES cells would be very useful in agricultural production of transgenic cows and may also have the potential for generating tissues and organs for use in cross species (xenotransplantation) to treat human diseases.

Primate Embryonic Stem Cells [2]

Primate ES-like cells have been derived from both the rhesus monkey (Thomson et al., 1995) and the common marmoset (Thomson et al., 1996). When allowed to grow to confluence and pile up, both marmoset and rhesus ES cells spontaneously differentiate into more complex structures, including cardiac muscle, neurons, endoderm, trophoblast, and numerous unidentified cell types (Thomson and Marshall 1998).

Essential characteristics of these primate ES-like cells include: 1) derivation from the preimplantation or peri-implantation embryo; 2) prolonged undifferentiated proliferation; and 3)

1 stable developmental potential to form derivatives of all three embryonic germ layers even after
2 prolonged maintenance in culture (Thomson and Marshall 1998). In addition, while mouse ES
3 cells rarely contribute to trophoblast in chimeras (Beddington and Robertson 1989), primate ES
4 cells differentiated into all three germ layers and trophoblast-like cells (Thomson and Marshall
5 1998). Furthermore, some primate ES cell lines have maintained a normal karyotype through
6 undifferentiated culture for at least two years, sustained a stable developmental potential
7 throughout this culture period, and maintained the potential to form trophoblast *in vitro*
8 (Thomson et al., 1995, 1996).

10 Although there is some variation between species, nonhuman primate ES cell lines seem
11 to provide a good *in vitro* model for understanding the differentiation of human tissues (Thomson
12 and Marshall, 1998). In addition, primate ES cells provide a powerful model for understanding
13 human development and disease. Furthermore, because of the similarities between ES cells from
14 humans and primates, primate ES cells provide a good model for developing strategies to prevent
15 immune rejection of transplanted cells and for demonstrating the safety and efficacy of ES cell-
16 based therapies (Thomson, et al., 1995).

17 **Human Models [1]**

18 **Human Embryonic Stem Cell Lines Derived from Blastocysts [2]**

19 The first successful isolation of cells from the human inner cell mass of blastocysts and
20 their culture *in vitro* for at least two passages was reported by Bongso and colleagues in 1994
21 (Bongso et al., 1994). Starting with 21 spare embryos donated by 9 patients in an IVF program²,
22 this group isolated cells with typical stem cell characteristics from 17 5-day-old blastocysts
23 (approximately 100 cells) (Bongso et al., 1994). These cells were like ES cells—small and round
24 with high nuclear to cytoplasmic ratios, stained positively for alkaline phosphatase (a
25 biochemical marker for stem cells), and maintained a normal diploid karyotype—however, after
26 the second subculture, the cells differentiated into fibroblasts or died (Bongso et al., 1994).

28 In later work, Thomson and his colleagues were able to isolate human ES-like cell lines
29 and grow them continuously in culture for at least five to six months. Although these cells have

1 not passed the most stringent test—as have mouse ES cells—to determine if they can contribute
2 to the germ line, we will continue to use the term “human ES cell” throughout this report because
3 it has been widely applied by both scientists and non-scientists in reference to these cells. This
4 renewable tissue culture source of human cells, capable of differentiating into a wide variety of
5 cell types, is believed to have broad applications in basic research and transplantation therapies
6 (Gearhart 1998).

7
8 In Thomson’s work human ES cells were isolated from embryos that were originally
9 produced by *in vitro* fertilization (IVF) for clinical reproductive purposes (see Box 2-B).
10 Individuals through a careful informed consent process donated the embryos and the entire
11 protocol was reviewed and approved by an appropriately constituted Institutional Review Board
12 (Thomson et al., 1998). Thirty-six embryos were cultured for approximately five days. The inner
13 cell mass was isolated from 14 of the 20 blastocysts that developed, and 5 ES cell lines,
14 originating from 5 separate embryos, were derived (Thomson et al., 1998). The technique used to
15 derive these human ES cells was essentially the same as that used to isolate nonhuman primate
16 ES cell lines (Thomson et al., 1995).

17
18 The resulting human ES cell lines had normal karyotypes (two male and three female),
19 and were grown in culture continuously for at least five to six months (Thomson et al., 1998). In
20 addition, the cell lines expressed cell surface markers that are also found on nonhuman primate
21 ES cells (Thomson et al., 1998). Most importantly, the cell lines maintained the potential to form
22 derivatives of all three embryonic germ layers, endoderm, mesoderm, and ectoderm (Thomson et
23 al., 1998).

24
25 It is believed that research with human ES cells could offer insights into developmental
26 events that cannot be studied directly in the intact human embryo, but that have important
27 consequences in clinical areas, including birth defects, infertility, and pregnancy loss. It is also
28 speculated that the origin of many human diseases (e.g., juvenile onset diabetes) are due to events
29 that take place very early in embryonic development. Such cells will also be particularly
30 valuable for the study of the development and function of tissues that differ between mice and

humans. Importantly, these cells allow for studies that focus on understanding the differentiation of cells into specific tissues, and understanding the factors that bring about differentiation so that cells can be manipulated to generate specific cell types for therapeutic transplantation. Moreover, it may be possible to identify gene targets for new drugs, manipulate genes that could be used for tissue regeneration therapies, and understand the teratogenic or toxic effects of certain compounds (Thomson et al., 1998).

Box 2-B: *In vitro* Fertilization

The procedure of *in vitro* fertilization of human oocytes is now widely available in many countries throughout the world including the United States. It was originally developed for the treatment of infertility due to blocked fallopian tubes, but has been extended to assist patients with premature depletion of oocytes, recurrent failure of embryos to implant, and low production of functional sperm. More recently, the technique has been used in conjunction with preimplantation genetic diagnosis to enable fertile couples at risk for transmitting severe or fatal inherited diseases to have healthy children.

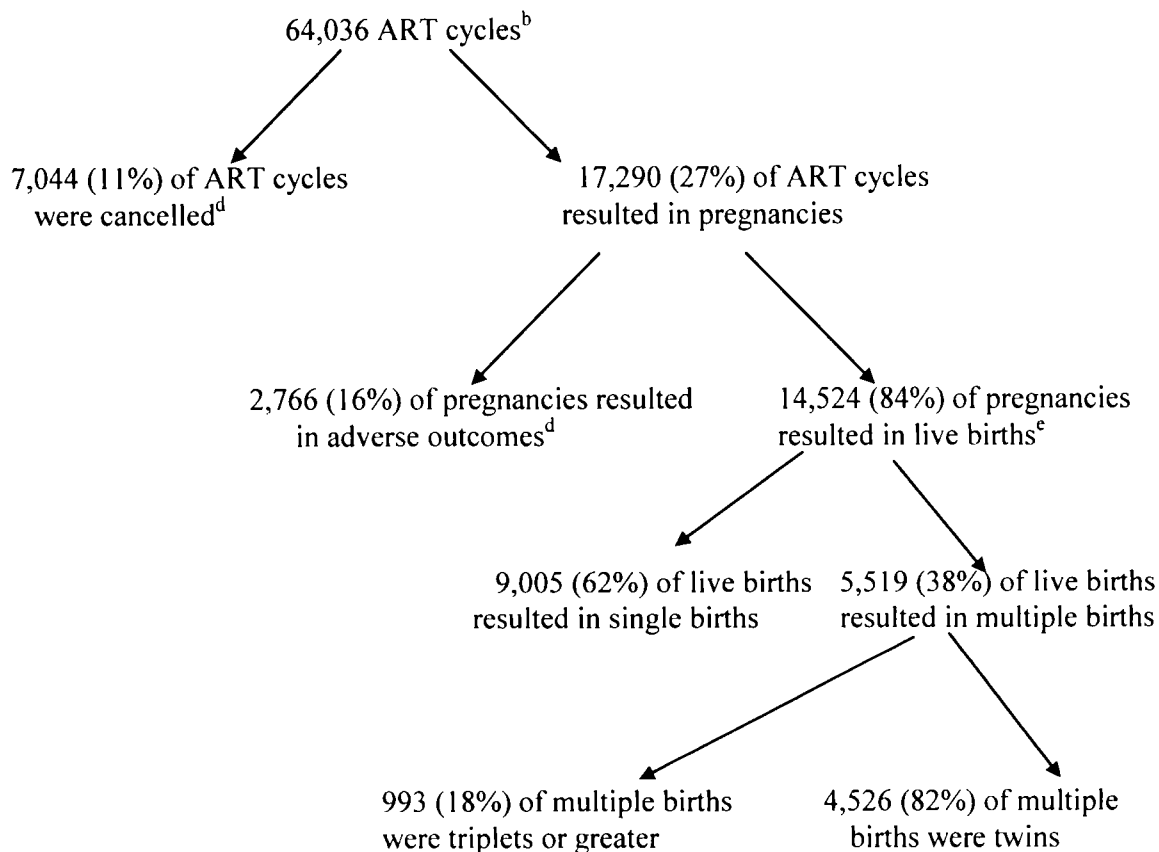
Although details of the IVF procedures vary among centers, the basic principles are as follows: oocyte donors are treated with a regimen of hormones over several days designed to stimulate the final maturation of several follicles within the ovary. This is known as hyperstimulation, and carries with it a low risk (less than 1 in 100) of an adverse reaction. Following completion of the hormone treatment mature follicles are detected by sonography and an average of around 10 are collected by transvaginal aspiration under sedation. The oocytes are then fertilized by sperm collected from a male donor and cultured in sterile fluid for about two days. When the zygote has reached the 4- to 8-cell stage, between 3 and 6 zygotes are transferred to the uterus, and untransferred embryos are usually frozen, if they are developing normally. Non-viable embryos are discarded. (See also Figure 1.) More recently, IVF specialists have begun culturing embryos to the blastocyst stage before transfer to the uterus?

The efficiency of the IVF procedure is relatively low, with approximately 5 to 10 percent of fertilized eggs giving rise to live born infants, depending on factors such as age of the recipient and the reason for infertility. In comparison, approximately 30 percent of normally conceived human

embryos result in a successful pregnancy. Embryos not transferred can be cryopreserved and stored indefinitely.

SOURCES: Report of the NIH Human Embryo Research Panel, 1994; *Assisted Reproductive Technologies: Analysis and Recommendations for Public Policy*, The New York State Task Force on Life and the Law, 1998.

Figure 2-1: 1996 Assisted Reproductive Technology Success Rates^a



^aFrom: Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, and RESOLVE. 1998. 1996 Assisted Reproductive Technology Success Rates, National Summary and Fertility Clinic Reports, December 1998.

^bData are from 300 U.S. fertility clinics that provided and verified information about the outcomes of all assisted reproductive technology (ART) cycles started in their clinics in 1996.

^cFresh, nondonor cycles were canceled, most commonly because too few (egg) follicles developed. Illness unrelated to the ART procedure may also lead to cancellation. In general, cycles are canceled when chances of success are poor or risks are unacceptably high.

^dAdverse outcomes included spontaneous abortion (83%), induced abortion (10%), stillbirth (4%) or ectopic pregnancy (3%).

^eA total of 20,659 babies were born as a result of the 64,036 ART cycles carried out in 1996.

Human Embryonic Germ Cells from Fetal Primordial Germ Cells [2]

Primordial germ cells can also give rise to cells with characteristics of ES cells, and, as discussed previously, have been designated *embryonic germ (EG) cells* to distinguish their tissue of origin (Gearhart 1998). A 1998 report from John D. Gearhart of the Johns Hopkins University School of Medicine in Baltimore and his colleagues describes the establishment of human EG cell lines from human primordial germ cells (Shamblott et al., 1998). The human EG cells were isolated from the developing gonads of 5- to 9-week old fetuses that were obtained as a result of elective abortion, using an IRB-approved protocol (Shamblott et al., 1998). These human EG cell lines have morphological, immunohistochemical, and karyotypic features consistent with those of previously described ES cells and have a demonstrated ability to differentiate *in vitro* into derivatives of the three embryonic germ layers (Shamblott et al., 1998).

Fusion of Human Somatic Cells with Cow Eggs to Create Hybrid Embryonic Cells [2]

Advanced Cell Technology of Worcester, Mass. announced in a November 11, 1998 press release, that its scientists had made human somatic cells revert to the primordial state by fusing them with cow eggs to create a hybrid embryo (Wade 1998). This work with human cells was performed in 1996 by Jose Cibelli. Using 52 of his own cells, some of them white blood cells and others scraped from the inside of his cheek, Cibelli used a pulse of electricity to fuse each cell with a cow egg from which the nucleus containing the DNA had first been removed, the details of which were described in a European patent application (PCT/U397/12919, 1997). Out of these 52 attempts, only one embryo, derived from a cheek epithelial cell, developed into a blastocyst. Approximately 12 days after the fusion of cheek cell and cow egg, there were sufficient cells to allow harvesting of the inner cell mass to produce cells resembling human ES cells (PCT/U397/12919, 1997). The scientists observed that the hybrid cell quickly became more human-like as the human nucleus took control and displaced cow proteins with human proteins. However, it is difficult to judge the validity of this work and the nature of the “embryo-like” material produced since it is extremely preliminary and has not been submitted for peer review or publication in a scientific journal.

1 The stated purpose of these experiments was to create an embryo solely for the purpose of
2 establishing an ES cell line that could potentially be used to treat any disease caused by loss or
3 malfunction of cells, such as Parkinson's disease, diabetes, and heart disease. The researchers
4 emphasized that they had no intention of transferring the resulting hybrid embryos to a uterus,
5 something they considered to be unethical and unsafe (Wade 1998).

7 **Growth and Derivation of Embryonic Stem Cells [1]**

8 Human ES cells are different from many adult cells in that they have the ability to divide
9 extensively in culture. Although this property has been interpreted by non-scientists as meaning
10 that investigators can simply use existing human ES and EG cell lines to study their properties,
11 this is a misunderstanding of the science. Evidence from mouse ES cell research suggests that it
12 is essential to derive ES cells in order to further our understanding of how to differentiate these
13 cells and grow them extensively in culture.

15 There are several reasons why repeatedly deriving ES cells is necessary. First, the
16 properties of ES cells differ depending on the method used to derive them.³ Cells derived under
17 some conditions may be limited in their potential to differentiate into a particular tissue type.

19 Second, ES cells are not stable cell types that can simply be mass-produced and supplied
20 to an unlimited number of researchers. As these cells grow in culture they accumulate
21 irreversible changes, and the conditions used to grow them can influence the speed at which
22 these changes accumulate. In one careful study the ability of ES cells to generate *all* tissue in a
23 mouse was tested (Nagy et al., 1993). Typically researchers only look at the ability of ES cells to
24 contribute to some tissues. The results dramatically showed that existing cell lines commonly in
25 use by many researchers had lost the ability to generate all mouse tissues and thus to completely
26 generate live mice. When new ES cells were derived and grown for only a short time in culture,
27 they did allow all tissues to be generated. However, after about 14 doublings in culture even
28 these cells lost their ability to contribute to all tissues. The authors conclude "...[P]rolonged
29 passage in culture reduces the potential of the ES cell population as a whole. [T]he proportion of
30 cells that retain full potential diminishes with extended passage" (Nagy et al., 1993). Exactly

1 what changes occur during culture is not yet clear. The chromosome complement remains
2 normal, indicating that this criterion, although frequently used to characterize ES cells, is not a
3 very stringent assay. It could be an accumulation of mutations, changes in gene expression, or
4 epigenetic changes (Nagy et al., 1993). Thus if one scientist were to obtain cells from a
5 colleague, the properties of the cells would depend greatly on the history of how those cells were
6 grown. For this reason, many people who work with mouse ES cells re-derive the cells
7 periodically to be sure they have the potential to differentiate into or contribute to many different
8 tissues.

9
10 Finally, perhaps the most important reason for deriving ES cells rather than simply
11 working with existing cell lines is that there is a tremendous amount to be learned in the process
12 of derivation itself. It took many laboratories over 10 years to work out conditions for the
13 derivation and growth of mouse ES cells. Research on the growth and derivation of ES cells from
14 other mammalian species is only in its early stages. In fact, only mouse ES cells have the
15 property of contributing to the germline cell lineage, the most stringent criterion for ES cells.
16 Thus cells from other species are referred to as ES-like cells (Pedersen 1994). Thus further basic
17 research into the proper conditions to maintain ES cells from many species is ongoing to try to
18 understand the factors necessary to generate truly stable ES cells. Given that only two successes
19 have so far been reported on the derivation of human ES and EG cells, it is likely that significant
20 basic research into to appropriate conditions to generate stable stem cells will be necessary.

21 22 **Potential Medical Applications of Human Embryonic Stem Cell and Embryonic Germ Cell** 23 **Research [1]**

24 Although research into the use of ES and EG cells is still at an early stage, there are a
25 large number of areas in which researchers hope to make a contribution to disease treatment. The
26 ability to elucidate the mechanisms that control cell differentiation is, at the most elemental level,
27 the promise of human ES and EG cell research. This knowledge will facilitate the efficient,
28 directed differentiation of stem cells to specific cell types. The standardized production of large,
29 purified populations of, for example, human cells such as cardiomyocytes and neurons could
30 provide a substantial source of cells for drug discovery and transplantation therapies (Thomson et

al., 1998). Many diseases, such as Parkinson's disease and juvenile-onset diabetes mellitus, result from the death or dysfunction of just one or a few cell types and the replacement of those cells could offer lifelong treatment.

Substantial advances in basic cell and developmental biology are required, however, before one could direct human ES cells to lineages of human clinical importance. However, progress has already been made in the differentiation of mouse ES cells to neurons, hematopoietic cells, and cardiac muscle (Deacon 1998; Brustle 1997; Shambloott 1998). Human ES and EG cells could be put to use in targeting neurodegenerative disorders, diabetes, spinal cord injury, and hematopoietic repopulation. Current treatments for these disorders are either incomplete or create additional complications for those who suffer from them.

Use of Human Embryonic Stem Cells and Embryonic Germs Cells in Transplantation [2]

One of the major causes of organ transplantation and graft failure is immune rejection. A likely application of human ES and EG cell research is in the area of transplantation. Although much research remains to be done, ES cells derived via somatic cell nuclear transfer offer the possibility that therapies could be developed from the patient's own cells, that is, a patient's somatic cell could be fused with an enucleated ova, developed to the blastocyst stage, at which point ES cells could be derived for the development of cell-based therapy, essentially an autologous transfer. Thus, issues of tissue rejection due to foreign proteins being recognized by the immune system are entirely avoided. In addition, research to establish xenotransplantation (i.e., interspecies transplantation) as a safe and effective alternative to human organ transplantation is still in its infancy. Alternatively, other techniques could potentially be used to generate stem cells that would be immunologically compatible for transplantation purposes, such as:

- 1) banking of multiple cell lines representing a spectrum of major histocompatibility complex (MHC) alleles to serve as a source for MHC matching; and/or
- 2) creation of universal donor lines, in which the MHC genes could be genetically altered so rejection would not occur, an approach that has been tried with moderate success in the mouse (NIH 1999).

Autologous transplants would obviate the need for immunosuppressive agents in transplantation and the ensuing susceptibility to other diseases. In addition to eliminating the need for immunosuppressive drugs, this would address problems ranging from the supply of donor organs to the difficulty of finding matches between donors and recipients. Research on ES cells could lead to cures for diseases that require treatment through transplantation, including autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and type-I diabetes (Varmus 1998; Juvenile Diabetes Foundation 1998). Treatment of type-I diabetes would involve the transplantation of pancreatic islet cells or beta cells produced from autologous embryonic stem cells. These cells would enter the pancreas and provide normal insulin production by replacing the failing resident islet cells.

Studies of Human Reproduction and Developmental Biology [2]

Research using human ES and EG cells could offer insights into developmental events that cannot be studied directly in the intact human embryo but that have important consequences in clinical areas, including birth defects, infertility, and pregnancy loss (Thomson et al., 1998). ES and EG cells provide large quantities of homogeneous material that can be used for biochemical analysis of the patterns of gene expression and the molecular mechanisms of embryonic differentiation.

Cancer Therapy [2]

Human ES and EG cells may be used to reduce the tissue toxicity brought on by cancer therapy (NCI 1999). Already bone marrow stem cells, representing a more committed stem cell, are used to treat patients after high-dose chemotherapy. However, the recovered blood cells appear limited in their ability to recognize abnormal cells such as cancer cells. It is possible that injections of ES and EG cells would revive the complete immune response to patients undergoing bone marrow transplantation. Current approaches aimed at manipulating the immune system after high dose chemotherapy, so that it specifically recognizes cancer cells, have not yet succeeded.

Diseases of the Nervous System [2]

Some believe that in no area of medicine are the potential benefits of ES and EG cell research greater than in diseases of the nervous system (Senate testimonies, Gearhart, Varmus). The most obvious reason is that so many of these diseases result from the loss of nerve cells, and mature nerve cells cannot divide to replace those that are lost. For example, in Parkinson's disease, nerve cells that make the chemical dopamine die; in Alzheimer's disease, it is the cells that make acetylcholine that die; in Huntington's disease the cells that make GABA die, in multiple sclerosis, cells that make myelin die; in amyotrophic lateral sclerosis the motor nerve cells that activate muscles die. In stroke, brain trauma, spinal cord injury, and the many causes of cerebral palsy and mental retardation, numerous types of cells are lost with no built-in mechanism for replacing them.

Preliminary results from fetal tissue transplantation trials for Parkinson's disease suggest that supplying new cells to a structure as intricate as the brain can slow or stop disease progression (Freed 1999). Yet the difficulty of obtaining enough cells of the right type, that is, dopamine producing nerve cells—limits the application of this therapy. In 1999, scientists developed methods in animal models to isolate dopamine precursor cells from the dopamine – producing region of the brain and coax them to proliferate for several generations in cell culture. When these cells were implanted into the brains of rodents with experimental Parkinson's disease, the animals showed improvements in their movement control (NINDS 1999). Scientists have also learned to instruct a stem cell from even a non-dopamine region to make dopamine (Wagner, et al., 1999). A large supply of “dopamine competent” stem cells, such as ES cell lines, could remove the barrier of limited amounts of tissue. (See Box 2-C). Other diseases that might benefit from a similar approach are spinal cord injury, epilepsy, multiple sclerosis, stroke, and pediatric causes of cerebral palsy and mental retardation. In mice, neural stem cells have already been shown to be effective in replacing cells and genes throughout the brain, at multiple ages (Snyder, Taylor, and Woolfe 1995; Snyder et al., 1997; Rosario et al., 1997; Yandava, Billingham, and Snyder, 1999; Lacorazza et al., 1996). Engraftable human neural stem cells have also recently been isolated (Flax et al., 1998).

Box 3-C: Potential Treatment for Parkinson's Disease

Parkinson's disease is a degenerative brain disease that affects 2 percent of the population over age 70. Symptoms include slow and stiff movements, problems with balance and walking, and tremor. In more advanced cases, the patient has a fixed, staring expression, walks with a stooped posture and short, shuffling pace, and has difficulty initiating voluntary movements. Falls, difficulty swallowing, incontinence, and dementia may occur in the late stages. Patients often lose the ability to care for themselves and may become bedridden.

The cause of this illness is a deficiency of the neurotransmitter dopamine in specific areas of the brain. Treatment with drugs such as levodopa often is very effective in relieving the symptoms. However, as the disease progresses, treatment often becomes more problematic, with irregular responses, difficulty adjusting doses, and the development of side effects such as involuntary writhing movements. Brain surgery with transplantation of human fetal tissue has shown promise as therapy.

Stem cell transplantation may also be a promising therapy for Parkinson's. Injection of stem cells that can differentiate into brain cells may offer a means of replenishing neurons capable of synthesizing the deficient neurotransmitter, dopamine. It is possible that stem cell transplantation may be simpler and more readily available than fetal tissue transplantation.

Diseases of the Bone and Cartilage [2]

Because ES and EG cells constitute a relatively self-renewing population of cells, they can be cultured to generate greater numbers of bone or cartilage cells than could be obtained from a tissue sample. If a self-renewing, but controlled, population of stem cells can be established in a transplant recipient, it could effect long-term correction of many diseases and degenerative conditions in which bone or cartilage cells are deficient in numbers or defective in function. This could be done either by transplanting ES and EG cells to a recipient, or by genetically modifying a person's own stem cells and returning them to the marrow. Such an approach holds promise for the treatment of genetic disorders of bone and cartilage, such as osteogenesis imperfecta and the various chondrodysplasias. In a somewhat different potential

1 application, stem cells could perhaps be stimulated in culture to develop into either bone or
2 cartilage-producing cells. These cells could then be introduced into the damaged areas of joint
3 cartilage in cases of osteoarthritis, or into large gaps in bone that can arise from fractures or
4 surgery. This sort of repair would have a number of advantages over the current practice of tissue
5 grafting (NIAMS 1999).

6 7 **Blood Disorders [2]**

8 The globin proteins are essential for transport of oxygen in the blood. Different globins
9 are expressed at different developmental stages. The epsilon globin gene is expressed only in
10 embryonic red blood cells. When this gene—which is not normally expressed in the adult—is
11 artificially turned on in sickle cell patients, it blocks the sickling of the cells that contain sickle
12 cell hemoglobin. Research involving ES cells could help answer questions about how to turn on
13 the epsilon globin gene in adult blood cells and thereby halt the disease process. Stem cell
14 research may also help produce transplantable cells that would not contain the sickle cell
15 mutation.

16 17 **Toxicity and Drug Testing [2]**

18 Human stem cell research offers promise for use in testing the beneficial and toxic effects
19 of biologicals, chemicals and drugs in the most relevant species for clinical validity, humans.
20 Such studies could lead to fewer, less costly, better designed human clinical trials yielding more
21 specific diagnostic procedures and more effective systemic therapies. Beyond the drug
22 development screening of pharmacological agents for toxicity and/or efficacy, human stem cell
23 research could define new research approaches for clarifying the complex association of
24 environmental agents with human disease processes (NIEHS 1999). It also makes possible a new
25 means of conducting detailed investigations of the underlying mechanisms of the effects of
26 environmental toxins or mixtures of toxins, including their subtle effects on the developing
27 embryonic and fetal development tissue systems.

28 29 **Transplantable Organs [2]**

30 Several researchers are investigating ways to isolate adult stem cells and create

transplantable organs that may be used to treat a multitude of diseases that do not rely on the use of embryonic or fetal tissue. Moreover, if it is found to be possible to differentiate embryonic stem cells into specific cell types, such stem cells could be an important source of cells for organ growth. For example, recent developments in animals have shown that it may be possible to create entire transplantable organs from a tissue base in a manner that would overcome such problems as the limited supply of organs and tissue rejection. If such a tissue base could be produced by directing the growth of human embryonic cells, this has the potential to be a major breakthrough.

For example, using tissue engineering methods, researchers have successfully grown bladders in the laboratory, implanted them into dogs, and shown them to be functional (Oberpenning et al., 1999). To create the bladders, small biopsies of tissue were taken from dog bladders which were teased apart to isolate the urothelial tissue and muscle tissue which were then grown separately in culture (Tanne 1999). The tissue was then applied to a mold of biodegradable material with the urothelial tissue on the inside and the muscle tissue on the outside. The new organs were transplanted within five weeks (Tanne 1999).

Dogs that received the tissue-engineered organs regained 95 percent of their original bladder capacity, were continent, and voided normally. When the new organs were examined 11 months later, they were completely covered with urothelial and muscle tissue, and had both nerve and blood vessel growth. Dogs who did not undergo reconstructive procedures or only received implants of the biodegradable molds did not regain normal bladder function (Oberpenning et al., 1999).

This accomplishment marks the first time a mammalian organ has been grown in a laboratory. The ability to create new organs by seeding molds with cells of specific tissue types would be extremely useful to treat babies with congenital malformations of organs and people who have lost organs due to trauma or disease (Tanne 1999).

Summary [1]

Currently, human ES cells can be derived from the inner cell mass of a blastocyst (those

1 cells within the conceptus that form the embryo proper) and EG cells from primordial germ cells
2 of fetuses. These cells, present in the very early stages of embryo and fetal development, can
3 generate all of the human cell types and are capable, at least for some time, of self-renewal. A
4 relatively renewable tissue culture source of human cells capable of being used to generate a
5 wide variety of cell types would have broad applications in basic research, transplantation, and
6 other important therapies. A major step in realizing this goal was taken in 1998 with the
7 demonstration that human ES and EG cells can be grown in culture. The clinical potential for
8 these stem cells is vast. Such cells will be important for in vitro studies of normal human
9 embryogenesis, abnormal development, human gene discovery, and drug and teratogen testing
10 and as a renewable source of cells for tissue transplantation, cell replacement, and gene therapies.
11

¹ Thompson, J.A. Public testimony before NBAC. January 19, 1999. Washington, D.C.

² Consent to carry out this study was approved by the hospital ethical committee based on the guidelines on Assisted Reproductive Technology of the Ministry of Health, Singapore that experimentation of human embryos up to day 14 of embryonic growth may be allowed (Bongso et al., 1994).

³ Hogan, B. NBAC Meeting. February 3, 1999. Princeton, N.J.

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Glossary

adult stem cells - stem cells found in the adult organism, for example, in bone marrow, skin, and intestine. These cells serve to replenish tissues where cells often have limited life span. They are more differentiated than are embryonic stem cells or embryonic germ cells.

blastocyst - a stage in the development of a mammalian embryo, which follows the morula. It consists of an outer layer of trophoblast to which is attached an inner cell mass.

blastomere - one of the cells into which the egg divides after its fertilization; one of the cells resulting from the division of a fertilized ovum.

cloning - the production of a precise genetic copy of a molecule (including DNA), cell, tissue, plant, or animal.

differentiation – the specialization of characteristics or functions of cell types.

diploid cell – the cell containing two complete sets of genes derived from the father and the mother respectively; the normal chromosome complement of somatic cells (in humans, 46 chromosomes).

ectoderm – the outer layer of cells in the embryo.

embryo - 1) the beginning of any organism in the early stages of development; 2) stage in prenatal development of a mammal between the ovum and the fetus; 3) in humans, stage of development between the 2nd and 8th weeks after fertilization inclusive

embryonic stem cell – cells derived from the inner cell mass of a blastocyst embryo.

embryonic germ cell – cells that are derived from precursors of germ cells from a fetus.

1 **endoderm** – the innermost of the three primary layers of the embryo.

3 **ex utero** – outside of the uterus

5 **fibroblast** – a cell present in skin and connective tissue, capable of forming collagen fibers.

7 **gamete** - 1) any germ cell, whether ovum or spermatozoon; 2) a mature male or female
8 reproductive cell.

10 **gastrulation** – the process of transformation of the blastula into the gastrula, at which point the
11 embryonic germ layers or structures begin to be laid out.

13 **germ cells** - gametes (ova and sperm) or the cells that give rise directly to gametes.

15 **GIFT (gamete intrafallopian tube transfer)** – In GIFT, a fiber-optic instrument called a
16 laparoscope is used to help place the unfertilized eggs and sperm (gametes) into the woman's
17 fallopian tubes through small incisions in her abdomen. Five percent of assisted reproductive
18 technology procedures used GIFT.

20 **haploid cell** – a cell with half the number of chromosomes as the somatic diploid cell, such as in
21 the ova or sperm. In humans the haploid cell has 23 chromosomes.

23 **in vivo** – in the natural environment, i.e., within the body.

25 **in vitro** – in an artificial environment, such as a test tube or culture media.

27 **IVF (in vitro fertilization)** – involves extracting a woman's eggs, fertilizing the eggs in the
28 laboratory, and then transferring the resulting embryo(s) into the woman's uterus through the
29 cervix. Roughly 70 percent of assisted reproduction attempts used IVF, using fresh embryos
30 developed from the woman's own eggs.

1 **karyotype** – the chromosome characteristics of an individual cell or of a cell line, usually
2 presented as a systematic array of metaphase chromosomes from a photograph of a single cell
3 nucleus arranged in pairs in descending order of size.

4
5 **mesoderm** – the middle of the three primary germ layers of the embryo; the origin of all
6 connective tissues, all body musculature, blood, cardiovascular and lymphatic systems, most of
7 the urogenital system, and the lining of the pericardial, pleural, and peritoneal cavities.

8
9 **morula** - 1) the mass of blastomeres resulting from the early cleavage divisions of the zygote; 2)
10 solid mass of cells resembling a mulberry, resulting from cleavage of an ovum.

11
12 **oocyte** - 1) a diploid cell that will undergo meiosis (a type of cell division of germ cells) to form
13 an egg; 2) immature ovum.

14
15 **ovum** - female reproductive or germ cell.

16
17 **pluripotent cells** - cells, present in the early stages of embryo development that can generate all
18 of the cell types in a fetus and in the adult and are capable of self-renewal. Pluripotent cells are
19 not capable of developing into an entire organism. [do we want to leave this in the glossary even
20 though we have said we are not using this term in our report?]

21
22 **preimplantation embryo** – 1) the embryo before it has implanted in the uterus; 2) commonly
23 used to refer to in vitro fertilized embryos before they are transferred to a woman's uterus.

24
25 **somatic cells** - [from *soma* - the body] 1) cells of the body which in mammals and flowering
26 plants normally have 2 sets of chromosomes, one derived from each parent; 2) all cells of an
27 organism with the exception of the germ cells.

28
29 **stem cell** - cells that have the ability to divide indefinitely and to give rise to specialized cells as
30 well as to new stem cells with identical potential.

1 **totipotent** - means the potential is total; having unlimited capacity. Totipotent cells have the
2 capacity to differentiate into the embryo and into extraembryonic membranes and tissues.
3 Totipotent cells contribute to every cell type of the adult organism. [do we want to leave this in
4 the glossary even though we have said we are not using this term in our report?]

5
6 **trophoblast** - The outermost layer of the developing blastocyst of a mammal. It differentiates
7 into two layers, the cytotrophoblast and syncytiotrophoblast, the latter coming into intimate
8 relationship with the uterine endometrium with which it establishes nutrient relationships.

9
10 **zygote** - 1) the cell resulting from the fusion of two gametes in sexual reproduction; 2) a
11 fertilized egg (ovum); 3) the diploid cell resulting from the union of a sperm and ovum; 4) the
12 developing organism during the first week after fertilization.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Larry Miike <lhmiike@aloha.com> (Larry Miike <lhmiike@aloha.com> [UNKNOWN])

CREATION DATE/TIME:30-JUL-1999 18:59:54.00

SUBJECT: Re: chapter 1

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

My comments, too, are only editorial in nature. The chapter is nicely concise.

Page 1:

the second sentence is really a parenthetical thought and should be enclosed in parentheses

In the sentence on Thomson's work (is his name spelled with a "p" or not?), either "embryo" should be plural, or "couples" should be singular, and if embryo is singular, then the preceding "a" should be an "an." I don't know which is correct, as i don't know if more than one couple's embryos were involved.

sentence describing the third purported research -- i continue to be of the opinion that we shouldn't distinguish this newspaper article by calling it a "report." I would call it an "article."

second paragraph: put a comma between "body" and "there."

Page 2.

middle of first paragraph: "specialized cells or tissue" -- need to make tissue plural.

Page 8.

Paragraph beginning "Since there are several sources of ES cells, we decided that it should..." To whom or what does the "it" refer? i would rewrite this to delete the "it."

Page 9.

comma between "treatment" and "requires" in the last sentence of the first full paragraph.

larry

-----Original Message-----

From: Hanna, Kathi (OD) <HannaK@od.nih.gov>

To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>

Date: Thursday, July 29, 1999 8:50 AM

Subject: chapter 1

>Attached for your review is the next version of chapter 1 of the stem cell
>report. We will be sending chapters out as they become available. Please

try to

>get your responses and comments back on this chapter by Monday, August 2.

As

>always, please call if you would like a fax or hard copy version. The

person to

>call is Kerry Jo Lee at 301-402-4242.

>

>Thanks,

>

>Kathi

>

> <<sc ch1 7-29.doc>>

>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: TRISH@NH1.NH.PDX.EDU (TRISH@NH1.NH.PDX.EDU [UNKNOWN])

CREATION DATE/TIME:30-JUL-1999 14:21:56.00

SUBJECT: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

I'm not sure, Kathi, what you mean by COB. I always thought a cob was a rather stocky riding horse. Anyway, I have a few moiror remarks about chapter 1 (I think it looks good), which is the only chapter I've received so far (my chapters are being faxed, I am still unable to download email attachments).

I suspect that we may want to keep some continuity between our reports. In our "Capacity" report we refer to ourselves as NBAC. Shouldn't we do the same in this report?

See references to us as 'commission' on the following pages: p. 5, line 16; p.6, lines 5 and 13; p. 7, line 22; and p. 9, lines 10 and 22.

p. 7, line 2, if I was a first time reader of this report, i think it would be helpful to know what 'different aspects of the problem' were addressed. Would it be too cumbersome to list them?

p. 7, line 10, I suggest that we delete 'valuing' and insert 'honoring'

p. 7. line 11, delete 'were' and insert 'are'

p. 7. line 22, use the present tense as in 'use'

p. 8. line 16, delete 'that it should' insert 'to'

p.8. line 17, delete 'that would' insert 'in order to'

I presume everybody has read the stem cell articles in yesterday's and today's NY Times.

I look forward to reading chapters 2 and 4.

Trish

Patricia Backlar
Research Associate Professor of Bioethics
Department of Philosophy
Portland State University

POB 751

Portland OR 97207-0751

telephone: 503/725-3499

fax: 503/725-3693 or 503/725-4882

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trish@nh1.nh.pdx.edu

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Kathi E. Hanna" <khanna@chesapeake.net> ("Kathi E. Hanna" <khanna@chesapeake.net> [UNKNOWN])

CREATION DATE/TIME:30-JUL-1999 14:55:59.00

SUBJECT: Re: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Trish: Thanks for your comments. At the last meeting , it was decided that we would avoid speaking of the Commission in the third person, with some exceptions. Our editor, Sara Davidson, will eventually make the style consistent.

Sorry, COB is short hand for "close of business" which is a relative term, I suppose. If you want to give me your comments via a stocky riding horse that would be exciting.

Kathi

----- Original Message -----

From: <TRISH@NH1.NH.PDX.EDU>

To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>

Sent: Friday, July 30, 1999 3:20 PM

Subject: stem cell report

> I'm not sure, Kathi, what you mean by COB. I always thought a cob was
> a rather stocky riding horse. Anyway, I have a few moiror remarks
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> Trish
>
>
> -----
> Patricia Backlar
> Research Associate Professor of Bioethics
> Department of Philosophy
> Portland State University
> POB 751
> Portland OR 97207-0751
> telephone: 503/725-3499
> fax: 503/725-3693 or 503/725-4882
> email: backlarp@pdx.edu
> or
> trish@nh1.nh.pdx.edu
>
>
>
>
>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: TRISH@NH1.NH.PDX.EDU (TRISH@NH1.NH.PDX.EDU [UNKNOWN])

CREATION DATE/TIME:30-JUL-1999 19:26:03.00

SUBJECT: Re: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Eric, I have now received chapter 2, but no sight of chapter 4, I'll have to wait till Monday.

Kathi, I remember our decision not to speak in the third person, but I was referring to the 'exceptions,' which had crept in. If there are to be exceptions I think it is clearer if we refer to ourselves as NBAC, rather than the commission (there are many commissions and it can become confusing).

Trish

> Date sent: Fri, 30 Jul 1999 14:56:42 -0400
> Send reply to: nbac-members@lists.Princeton.EDU
> From: "Kathi E. Hanna" <khanna@chesapeake.net>
> To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
> Subject: Re: stem cell report
> Originally to: <nbac-members@lists.Princeton.EDU>

> Trish: Thanks for your comments. At the last meeting , it was decided that
> we would avoid speaking of the Commission in the third person, with some
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> suppose. If you want to give me your comments via a stocky riding horse that
> would be exciting.
>
> Kathi
> ----- Original Message -----
> From: <TRISH@NH1.NH.PDX.EDU>
> To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
> Sent: Friday, July 30, 1999 3:20 PM
> Subject: stem cell report
>
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> > and today's NY Times.

> >

> > I look forward to reading chapters 2 and 4.

> >

> > Trish

> >

> >

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> > Patricia Backlar
> > Research Associate Professor of Bioethics
> > Department of Philosophy
> > Portland State University
> > POB 751
> > Portland OR 97207-0751
> > telephone: 503/725-3499
> > fax: 503/725-3693 or 503/725-4882
> > email: backlarp@pdx.edu
> > or
> > trish@nhl.nh.pdx.edu

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or
trish@nhl.nh.pdx.edu

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Rhetaugh <rhetaugh@umich.edu> (Rhetaugh <rhetaugh@umich.edu> [UNKNOWN])

CREATION DATE/TIME: 2-AUG-1999 20:33:18.00

SUBJECT: Re: chapter 1

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])

READ:UNKNOWN

TEXT:

I have read Chapter 1 and will not offer any futher changes.

Rhetaugh

--On Thursday, July 29, 1999, 2:48 PM -0400 "Hanna, Kathi (OD)"
<HannaK@od.nih.gov> wrote:

> Attached for your review is the next version of chapter 1 of the stem
cell
> report. We will be sending chapters out as they become available. Please
> try to get your responses and comments back on this chapter by Monday,
> August 2. As always, please call if you would like a fax or hard copy
> version. The person to call is Kerry Jo Lee at 301-402-4242.
>
> Thanks,
>
> Kathi
>
> <<sc ch1 7-29.doc>>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Page, Alice (OD)" <PageA@od.nih.gov> ("Page, Alice (OD)" <PageA@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME: 2-AUG-1999 11:15:30.00

SUBJECT: RE: International Project

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])

READ:UNKNOWN

TEXT:

While we are working on completing the stem cell report, NBAC staff is also looking toward the next report on international research and human subjects protections. In this regard, the attached memorandum summarizing the international project consultants' meeting held on July 14 in Cambridge is one of several items on which our efforts have been focused. Ruth Macklin is preparing a revised project outline, and staff is putting together a plan to implement the project and preparing for the NBAC meeting on September 16 and 17 in Washington, D.C. We expect to devote a substantial portion of that meeting to the international project. The consultants will be present and it is likely that you will hear testimony from additional experts at that time. Also, we hope to have the introductory chapter written by then for your review and comment.

We will, from time to time during the next month, provide updates on the project. If you have any questions or comments about the attached memorandum or the report in general, please feel free to call or email me.

Alice Page

<<Commissioner's Summary of 7.14.98 Jul 30.doc>>

- Commissioner's Summary of 7.14.98 Jul 30.doc===== ATTACHMENT 1
=====

ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:

Unable to convert ARMS_EXT:[ATTACH.D91]ARMS281957318.236 to ASCII,

The following is a HEX DUMP:

===== END ATTACHMENT 1 =====

MEMORANDUM

TO: NBAC Members
FROM: Alice Page, J.D., M.P.H.; Eric M. Meslin, Ph.D.
DATE: August 2, 1999
RE: Summary of International Project Consultants' Meeting, Cambridge, MA

As you know, following the NBAC meeting in Cambridge earlier this month, NBAC staff and consultants met to provide each other with status reports on projects underway, review the draft outline, and plan next steps in this project. Present were Ruth Macklin, Commissioner Alta Charo, NBAC staff members Eric Meslin, Alice Page, and Dan Powell, and consultants Elisa Eiseman, Liza Dawson, Nancy Kass, Patty Marshall, Jeremy Sugarman, and Noreen Teoh. This memorandum summarizes the status of the consultants' projects and discussion that followed regarding the draft outline prepared by Ruth Macklin.

A. Status of Consultants' Projects

Nancy Kass reported that her proposed study will collect data from U.S. researchers conducting human subjects research in "resource poor" countries through focus groups, in-depth interviews, and a mail survey. Preliminary pilot testing of the focus groups has suggested that they are likely to produce good data in government, the pharmaceutical industry, and with research scientists. The survey has encountered some delay in obtaining the necessary clearance through the White House Office of Management and Budget (a requirement that is part of the Paperwork Reduction Act). We expect that this will be resolved soon, but it will still take several months to complete the survey and analyze the data. If NBAC is not extended, plans are being made to provide summaries of the available data. A number of suggestions were made to supplement this data through general letters of inquiry (not questionnaires) to representatives from the private sector including the pharmaceutical and biotechnology industries, and schools of public health.

Elisa Eiseman has collected information from the RAND database RADIUS identifying federally sponsored human subjects research. Approximately 75 percent of the data has been collected to date and Elisa believes that she has identified the majority of the relevant studies. Privately funded research, however, is more of a problem in that it is more difficult to get and also may not be comprehensive. The RADIUS database does not have information regarding FDA regulated studies performed by private pharmaceutical companies. It was suggested that NBAC, through Dr. Shapiro, write the pharmaceutical companies to seek input on this issue. It was also suggested that the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Organization (BIO) be contacted seeking their participation in and support of this effort. Another suggestion was to ask representatives of pharmaceutical companies to provide testimony to NBAC. A list will be developed.

The question was asked whether the market value of the drugs being approved this year and the markets in which those drugs would be available correlated with the amount of research being done in those markets. If not, is the burden being placed on resource poor nations being fairly distributed? Another question was raised about whether the amount of research being done in other countries could be correlated with disease rates. If not, could this mean that researchers are doing research because of less stringent regulations?

Adnan Hyder was unable to attend the meeting but Nancy Kass discussed his study, which is to collect data from resource poor country researchers conducting human subjects research. Parallel to Nancy's study, Adnan's work will focus on the researchers' experiences with and attitudes towards U.S. Human Subject rules and regulations. To our knowledge, this is the first time a study of this nature has been conducted

Many wanted the study to include industrialized nations' responses to our regulations, in addition to those from resource poor nations. Because there are different concerns for these two groups, this will require a different survey to be sent out than that being used in Nancy and Adnan's studies. The current studies will not be able to fully provide information contrasting experiences of U.S. guidelines with those of other industrialized nations. However, information collected from the planned surveys and qualitative data may provide a good idea of the issues that are of a larger concern.

Commissioner Charo suggested that in light of the International Conference on Harmonization (ICH) on drugs, comparisons could be made on research guidelines, standards or regulations between the industrialized and developing countries, as well as between industrialized countries.

Jeremy Sugarman's project is focusing on eight case studies conducted around the world to determine how research is conducted, especially in collaboration with other countries. Broad preliminary themes that have emerged are:

- Compromise/negotiation versus conflict.
- Trust in the research enterprise.
- Troubles meeting documentation requirements.
- Desire for education regarding international guidelines.
- Different structures and processes for IRBs

There was a concern expressed by some present that the therapeutic misconception was particularly strong in other countries. Even if they try to convince subjects otherwise, researchers cannot dispel the notion that there will be some therapeutic benefit from participating in the research enterprise. Does this mean that an M.D. should not be doing the research, or that the research simply should not be done? In addition, in many countries, members of an IRB cannot meet together since such a meeting would be more political than scientific. What are the implications of this? In reviewing this work, it was stressed that these case studies cannot and should not be used

Comment [DP1]: Jeremy had deleted this from his revised copy, but I think it's important that we keep that in. Although it isn't in his project, I think this should reflect the rich discussion around that topic.

to make generalizations about research in any of the participating countries. However, these data should be useful in informing the commission's deliberations.

A draft report from this study will be available for the September NBAC meeting.

Patty Marshall reported on her study about the relevance of culture to informed consent in international research. Her study will provide two major contributions. First is a literature review on the nature of personhood in cross-cultural situations, as well as differing beliefs about autonomy and social agency. Second is an in-depth case study conducted in Nigeria involving three genetic-epidemiological studies (hypertension, breast cancer, and diabetes II). Four broad themes emerged from this study, including (1) the location of decisional authority and social agency, (2) beliefs about biomedical procedures, (3) the nature of the clinician/provider/patient relationships, as well as those between researchers in the home country and the sponsoring country, and (4) beliefs about the efficacy of treatment.

Patty's project summary will be completed in August.

B. Discussion of Draft Outline

Dr. Macklin discussed the draft outline. Major concerns include whether the report should be organized by issues or substantive ethical concepts, such as global justice, and problems with interpretations of the federal regulations. Another concern is the breadth of the scope of the project and its primary focus, both of which should be determined by the Commission. After our initial discussion, Dr. Macklin's proposed the following revised theme-based outline:

- **Disclosure to Research Subjects.** This discussion would include issues such as community involvement, informed consent, regulations, family involvement, written vs. oral consent, and the role of beliefs and attitudes of research subjects.
- **Risk/Benefit Considerations.** The main issue here is whether it is ethically acceptable to conduct a trial in a developing country when it would be unethical to do so in an industrialized country? Included would be a discussion of the burden of disease, economic conditions, and the risks of not performing the research.
- **Care and Treatment Owed to Research Subjects.** Is it obligatory to provide care that would be standard in the industrialized country? Would it be coercive to offer such treatment, or merely an inducement? If such an obligation exists, whose responsibility is it, and to whom is the responsibility owed?
- **Independent Review of Research.** Can local IRBs handle issues in developing countries or is a national IRB or other alternative needed?
- **Regulations.** This discussion would include substantive content issues (what U.S. regulations cover/don't cover) as well as difficulties in their application. How far can the regulations go in addressing these issues? There are issues arising from other factors that the regulations cannot adequately address. Thus recommendations must be included that go beyond the regulations.

- Issues of Global Justice. Where should this chapter be placed? Also, there was concern expressed that issues of justice should pervade the report, not simply be discussed in one chapter.

Alta Charo suggested an alternative outline, based on the following elements of culture:

- Culture of Science. Some cultures have little or no familiarity with randomization, the use of placebos, and the like. What does this say, if anything, about our insistence in exporting our protocols?
- Culture of Trust. In the U.S., provider/patient trust offsets the therapeutic misconception that (explain). Is this true in other countries? How does this play out in the informed consent context?
- Culture of Professionalism. Professional integrity and the protection of patients (e.g., peer review in form of IRBs) serve as a check on the research imperative. Is this research imperative present in other countries, or do we export it there? If it is not there, do we need IRBs?
- Culture of Care. What is owed and what is expected? There may be an expectation of care and treatment in other countries that is not present in the U.S.
- Culture of Paper. Auditing (in contrast to protection) generates piles of paperwork that must be maintained. What is the purpose of auditing? Is there an alternative?
- Culture of Resources. What expenditure of time and money is warranted?
- Culture of Justice

Jeremy Sugarman suggested that an additional element be added to the above list, the culture of safety (in contrast to the culture of fatalism).

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Powell, Dan (OD)" <PowellD1@od.nih.gov> ("Powell, Dan (OD)" <PowellD1@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME: 2-AUG-1999 10:24:32.00

SUBJECT: RE: International Project

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
There we go. :)

-- Dan

-----Original Message-----

From: Page, Alice (OD)
Sent: Monday, August 02, 1999 10:14 AM
To: NBAC Members E-list
Subject: RE: International Project

While we are working on completing the stem cell report,
NBAC
staff is
also looking toward the next report on international research and
human
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in Washington, D.C. We expect to devote a substantial portion of
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to the international project. The consultants will be present and
it is
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that you will hear testimony from additional experts at that time.
Also, we

hope to have the introductory chapter written by then for your
review
and
comment.

We will, from time to time during the next month, provide
updates on the
project. If you have any questions or comments about the attached
memorandum or
the report in general, please feel free to call or email me.

Alice Page

<<Commissioner's Summary of 7.14.98 Jul 30.doc>> << File:
Commissioner's Summary of 7.14.98 Jul 30.doc >>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Meslin, Eric (OD)" <MeslinE@od.nih.gov> ("Meslin, Eric (OD)" <MeslinE@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME: 3-AUG-1999 14:25:49.00

SUBJECT: RE: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Trish, could you say why you disagree with Tom regarding the Davis comments (so others will have a chance to understand what is at issue here).

Eric M. Meslin, Ph.D
Executive Director
National Bioethics Advisory Commission
6100 Executive Blvd. Suite 5B01
Rockville, Maryland 20892-7508
Tel: (301) 402-4242
Fax: (301) 480-6900
Email: MeslinE@OD.NIH.GOV
<http://www.bioethics.gov>

-----Original Message-----

From: TRISH@NH1.NH.PDX.EDU [SMTP:TRISH@NH1.NH.PDX.EDU]
Sent: Tuesday, August 03, 1999 2:02 PM
To: NBAC Members E-list
Subject: Re: stem cell report

Kathi, Eric, and staff, what I have seen of the report really looks good. My few 'me too' remarks are: I agree with Larry and Alex's opinions, and also believe that Jim and Tom's suggestions are useful and apt. However, I strongly disagree with Tom about deleting Dena's remarks on p. 22 lines 19-24.
Trish

> Date sent: Tue, 3 Aug 1999 06:56:35 -0700 (PDT)
> Send reply to: nbac-members@lists.Princeton.EDU
> From: Alex Capron <acapron@law.usc.edu>
> To: NBAC Members E-list
<nbac-members@lists.Princeton.EDU>
> Subject: Re: stem cell report
> Originally to: NBAC Members E-list
<nbac-members@lists.Princeton.EDU>

> i am just briefly back on e-mail and wanted belatedly to state

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> i largely agree with larry's point about our rising above the
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Patricia Backlar
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fax: 503/725-3693 or 503/725-4882
email: backlarp@pdx.edu
or
trish@nhl.nh.pdx.edu

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Thomas Murray <murrayt@thehastingscenter.org> (Thomas Murray <murrayt@thehastingscenter.org> [UNKNOWN])

CREATION DATE/TIME: 3-AUG-1999 17:14:43.00

SUBJECT: RE: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
Dear Trish,

I would want to see what we propose to add before I agree to it. I still think we should lose the sentence about disrespect as it is in its own way disrespectful of those who don't agree with Dena's take on this matter.

Tom

-----Original Message-----

From: owner-nbac-members@lists.Princeton.EDU
[mailto:owner-nbac-members@lists.Princeton.EDU]On Behalf Of
TRISH@NH1.NH.PDX.EDU
Sent: Tuesday, August 03, 1999 4:09 PM
To: NBAC Members E-list
Subject: RE: stem cell report

Yes, Dena does echo Meilaender's concern but as I read this paragraph she also eloquently responds to him by laying out precisely what those "concerns" may be. The paragraph refers only to Meilaender's concern that the "Commission...avoid misleading and even deceptive language...." Dena makes explicit what only is implicit in the way Meilaender's concerns are presented. That is why I suggest that we follow her quoted remarks, with something that indicates we are in accord with her argument

> Date sent: Tue, 3 Aug 1999 14:44:23 -0400
> Send reply to: nbac-members@lists.Princeton.EDU
> From: "Thomas Murray" <murrayt@thehastingscenter.org>
> To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
> Subject: RE: stem cell report
> Originally to: <nbac-members@lists.Princeton.EDU>

> Trish,
>

> Now I am confused. It seems to me that Dena's remarks are an echo of Gil
> Meilander's concerns, not a response to them.

>
> Tom

>
> -----Original Message-----
> From: owner-nbac-members@lists.Princeton.EDU
> [mailto:owner-nbac-members@lists.Princeton.EDU]On Behalf Of
> TRISH@NH1.NH.PDX.EDU
> Sent: Tuesday, August 03, 1999 2:38 PM
> To: NBAC Members E-list
> Subject: RE: stem cell report
>
>
> As I see it we use Dena's informal and "straight ahead" remarks to
> respond to Meilander's important concern (this concern, I suspect
> reflects accurately some elements of public opinion that
> regards us as a tool being used to promote certain interests). Her
> words make clear that we have no intention of playing footsie and
> obfuscating the ethical connections between use and derivation of
> stem cells. Even though the first sentence of the paragraph in
> question (p. 22, lines 6- 24) states what our intentions are,
> perhaps it would be wise to follow Dena's remarks with some kind of
> succinct agreement with her.
> Trish
>
>
>
>> Date sent: Tue, 3 Aug 1999 13:06:27 -0400
>> Send reply to: nbac-members@lists.Princeton.EDU
>> From: "Meslin, Eric (OD)" <MeslinE@od.nih.gov>
>> To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
>> Subject: RE: stem cell report
>> Originally to: "nbac-members@lists.Princeton.EDU"
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>> Eric M. Meslin, Ph.D
>> Executive Director
>> National Bioethics Advisory Commission
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>> <http://www.bioethics.gov>
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>> -----Original Message-----
>> From: TRISH@NH1.NH.PDX.EDU [SMTP:TRISH@NH1.NH.PDX.EDU]
>> Sent: Tuesday, August 03, 1999 2:02 PM
>> To: NBAC Members E-list
>> Subject: Re: stem cell report
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> > > To: NBAC Members E-list
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> > > Subject: Re: stem cell report
> > > Originally to: NBAC Members E-list
> > <nbac-members@lists.Princeton.EDU>
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> > Patricia Backlar
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> > -----
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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Meslin, Eric (OD)" <MeslinE@od.nih.gov> ("Meslin, Eric (OD)" <MeslinE@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME: 3-AUG-1999 14:26:27.00

SUBJECT: RE: Comments on Chapter 4

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Thanks Bernie for these timely comments.

Eric M. Meslin, Ph.D
Executive Director
National Bioethics Advisory Commission
6100 Executive Blvd. Suite 5B01
Rockville, Maryland 20892-7508
Tel: (301) 402-4242
Fax: (301) 480-6900
Email: MeslinE@OD.NIH.GOV
<http://www.bioethics.gov>

-----Original Message-----

From: Bernard Lo, M.D. [SMTP:bernie@itsa.ucsf.edu]
Sent: Tuesday, August 03, 1999 1:01 PM
To: NBAC Members E-list
Subject: Comments on Chapter 4

I think Chap 4 is very good and agree with the detailed
coments
of Jim and Tom. I have some suggestions regarding the arguments for
federal
funding on pages 30-31, where we do not really spell out how federal
funding
could be ebneficial or syndergistic. There are several important issues
that we
can address more fully:

1. Federal research will encourage basic research on the
biology of
stem cells, in addition to the product-oriented research typically
supported by
biotechnology firms. Biotechnology firms are understandably focused on
developing products that can be brought to market. However, in the long
run,
advances in the basic biology of stem cells - what are the conditions and
signals which lead stem cells to differentiate and what are detailed
mechanisms
of differentiation - are essential for therapeutic advances. Such basic
research will require long-term efforts, which traditionally have been

supported
by NIH funding.

2. Federal funding would attract top-rank scientists who are currently not working in the field. The availability of long-term research grants through NIH is likely to attract distinguished scientists who are not now working in the field of stem cell research and who would not be attracted by the short-term support for product-oriented research that is typically available through industry. [Is this argument valid? Is there evidence to support it from other fields of biomedical research?]

3. Research findings and materials derived on federal grants may be more likely to be shared with other researchers. Surveys suggest that researchers funded by industry may be less willing to share their findings and ideas candidly. Such reluctance may be caused by concerns about disclosing proprietary information about products under development. Furthermore, sharing of biological materials derived from industry funding may be less widespread because industry-supported researchers may attach conditions to the sharing of materials, such as ownership claims on future inventions related to the materials [IOM report Resource Sharing in Biomedical Research, page 81]. Thus federal funding may lead to more widespread dissemination of findings and sharing of materials, which ultimately may enhance scientific discoveries.

Bernard Lo, M.D.
Professor of Medicine
Room C-126
521 Parnassus Ave.
University of California San Francisco
San Francisco, CA 94143-0903
Ph: 415-476-5370
Fax: 415-476-5020

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Alex Capron <acapron@law.usc.edu> (Alex Capron <acapron@law.usc.edu> [UNKNOWN])

CREATION DATE/TIME: 3-AUG-1999 09:58:47.00

SUBJECT: Re: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])

READ:UNKNOWN

TEXT:

i am just briefly back on e-mail and wanted belatedly to state that i largely agree with larry's point about our rising above the politics of the situation to state what we think is right...and i also agree that we spend too much time on the agonized "balancing," though not so much that i disagree with our doing so

i also hope that by stating the argument well for the position we support we will actually help others to rise above the present political situation and i wish well to those who are talking with leaders in congress about this

i also think we must be careful to limit our recommendations to STEM CELL research and not make generalized statements about the embryo research ban, which we have not studied carefully and which would provide ammunition to those who will oppose our specific recommendations

alex

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: TRISH@NH1.NH.PDX.EDU (TRISH@NH1.NH.PDX.EDU [UNKNOWN])

CREATION DATE/TIME: 3-AUG-1999 17:12:54.00

SUBJECT: RE: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Yes, Dena does echo Meilaender's concern but as I read this paragraph she also eloquently responds to him by laying out precisely what those "concerns" may be. The paragraph refers only to Meilaender's concern that the "Commission...avoid misleading and even deceptive language...." Dena makes explicit what only is implicit in the way Meilaender's concerns are presented. That is why I suggest that we follow her quoted remarks, with something that indicates we are in accord with her argument

> Date sent: Tue, 3 Aug 1999 14:44:23 -0400
> Send reply to: nbac-members@lists.Princeton.EDU
> From: "Thomas Murray" <murrayt@thehastingscenter.org>
> To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
> Subject: RE: stem cell report
> Originally to: <nbac-members@lists.Princeton.EDU>

> Trish,
>
> Now I am confused. It seems to me that Dena's remarks are an echo of Gil
> Meilander's concerns, not a response to them.

> Tom

>
> -----Original Message-----
> From: owner-nbac-members@lists.Princeton.EDU
> [mailto:owner-nbac-members@lists.Princeton.EDU]On Behalf Of
> TRISH@NH1.NH.PDX.EDU
> Sent: Tuesday, August 03, 1999 2:38 PM
> To: NBAC Members E-list
> Subject: RE: stem cell report

>
> As I see it we use Dena's informal and "straight ahead" remarks to
> respond to Meilander's important concern (this concern, I suspect
> reflects accurately some elements of public opinion that
> regards us as a tool being used to promote certain interests). Her
> words make clear that we have no intention of playing footsie and
> obfuscating the ethical connections between use and derivation of
> stem cells. Even though the first sentence of the paragraph in
> question (p. 22, lines 6- 24) states what our intentions are,

> perhaps it would be wise to follow Dena's remarks with some kind of
> succinct agreement with her.
> Trish
>
>
>
>> Date sent: Tue, 3 Aug 1999 13:06:27 -0400
>> Send reply to: nbac-members@lists.Princeton.EDU
>> From: "Meslin, Eric (OD)" <MeslinE@od.nih.gov>
>> To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
>> Subject: RE: stem cell report
>> Originally to: "nbac-members@lists.Princeton.EDU"
>> <nbac-members@lists.Princeton.EDU>
>
>> Trish, could you say why you disagree with Tom regarding the Davis
> comments (so
>> others will have a chance to understand what is at issue here).
>>
>> Eric M. Meslin, Ph.D
>> Executive Director
>> National Bioethics Advisory Commission
>> 6100 Executive Blvd. Suite 5B01
>> Rockville, Maryland 20892-7508
>> Tel: (301) 402-4242
>> Fax: (301) 480-6900
>> Email: MeslinE@OD.NIH.GOV
>> <http://www.bioethics.gov>
>>
>> -----Original Message-----
>> From: TRISH@NH1.NH.PDX.EDU [SMTP:TRISH@NH1.NH.PDX.EDU]
>> Sent: Tuesday, August 03, 1999 2:02 PM
>> To: NBAC Members E-list
>> Subject: Re: stem cell report
>>
>> Kathi, Eric, and staff, what I have seen of the report really
>> looks good. My few 'me too' remarks are: I agree with Larry and
>> Alex's opinions, and also believe that Jim and Tom's suggestions
are
>> useful and apt. However, I strongly disagree with Tom about
deleting
>> Dena's remarks on p. 22 lines 19-24.
>> Trish
>>
>> > Date sent: Tue, 3 Aug 1999 06:56:35 -0700 (PDT)
>> > Send reply to: nbac-members@lists.Princeton.EDU
>> > From: Alex Capron <acapron@law.usc.edu>
>> > To: NBAC Members E-list
> <nbac-members@lists.Princeton.EDU>
>> > Subject: Re: stem cell report
>> > Originally to: NBAC Members E-list
> <nbac-members@lists.Princeton.EDU>
>>
>> > i am just briefly back on e-mail and wanted belatedly to state
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> > >
> > > alex
> > >
> > >
> > >

> > Patricia Backlar
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> > Department of Philosophy
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> > POB 751
> > Portland OR 97207-0751
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> > or
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> > -----
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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: TRISH@NH1.NH.PDX.EDU (TRISH@NH1.NH.PDX.EDU [UNKNOWN])

CREATION DATE/TIME: 3-AUG-1999 14:27:03.00

SUBJECT: Re: stem cell report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

Kathi, Eric, and staff, what I have seen of the report really looks good. My few 'me too' remarks are: I agree with Larry and Alex's opinions, and also believe that Jim and Tom's suggestions are useful and apt. However, I strongly disagree with Tom about deleting Dena's remarks on p. 22 lines 19-24.

Trish

> Date sent: Tue, 3 Aug 1999 06:56:35 -0700 (PDT)
> Send reply to: nbac-members@lists.Princeton.EDU
> From: Alex Capron <acapron@law.usc.edu>
> To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
> Subject: Re: stem cell report
> Originally to: NBAC Members E-list <nbac-members@lists.Princeton.EDU>

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