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SUBJECT: just to complicate things a little more

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READ:UNKNOWN

TEXT:
Turning Brain into Blood: A Hematopoietic Fate Adopted by Adult Neural Stem Cells in Vivo
Christopher R. R. Bjornson, * Rodney L. Rietze, *õ Brent A. Reynolds, M. Cristina Magli, Angelo L. Vescovi

Stem cells are found in various organs where they participate in tissue homeostasis by replacing differentiated cells lost to physiological turnover or injury. An investigation was performed to determine whether stem cells are restricted to produce specific cell types, namely, those from the tissue in which they reside. After transplantation into irradiated hosts, genetically labeled neural stem cells were found to produce a variety of blood cell types including myeloid and lymphoid cells as well as early hematopoietic cells. Thus, neural stem cells appear to have a wider differentiation potential than previously thought.

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Stem cells have been identified in adult tissues that undergo extensive

cell replacement due to physiological turnover or injury such as the hematopoietic, intestinal, and epidermal systems (1). These cells have been found in the central nervous system (CNS) (2), a tissue thought to be capable of extremely limited self-repair. CNS stem cells can generate the three major cell types found in the adult brain: namely, astrocytes, oligodendrocytes, and neurons (3). This is consistent with the view that the developmental potential of stem cells is restricted to the differentiated elements of the tissue in which they reside. However, some developmental peculiarities suggest certain cells may be able to differentiate into cell types that are not of the same dermal origin (4). Hence, we sought to determine whether neural stem cells (NSCs) could produce hematopoietic progeny.

A bone marrow (BM) repopulation assay (5) was used to test this hypothesis. Hematopoietic stem cells from unfractionated adult BM (107cells per animal) or NSCs cultured from either the embryonic or adult forebrain (106 cells per animal) (6) of ROSA26 mice were systemically injected into sublethally irradiated Balb/c recipient animals (7). ROSA26 animals were selected as the source of donor tissue because they are of a different immunological background than Balb/c and are transgenic for lacZ (8), which encodes for the Escherichia coli enzyme -galactosidase. Importantly, to eliminate possible contamination of NSCs with cells of mesodermal origin (9), we also injected clonally derived adult ROSA26 NSCs (Fig. 1).

Fig. 1. Cloning of adult ROSA26 CNS stem cells. (A) Single adult ROSA26 NSC plated in isolation in a single well (arrow). After (B) 1 and (C) 8 days, a cluster of cells formed, which was serially subcultured every 4 days to establish a continuous culture. (D) All cells expressed the NSC antigen, nestin. Differentiation was induced by plating a fraction of these cells in 1% fetal bovine serum, in the absence of growth factors. (E) The simultaneous detection of neurons [red; 25.3 ñ 0.9% of total cell number (TCN); n = 6, ñ SEM], astroglia (blue; 71.6 ñ 6.3% TCN; n = 6), and oligodendroglia (green; 0.9 ñ 0.01% TCN; n = 6) among the progeny of this cell indicate its tripotentiality (19). Secondary clones of the cell displayed in (A) produced an average of 48 ñ 3.2 (n = 6) cells capable of producing tertiary, tripotential clones, thereby demonstrating self-maintenance (2). Data are from clone 2H1. Bars: (A) to (C), 90 æm; (D), 60 æm; (E), 40 æm. [View Larger Version of this Image (114K GIF file)]

Polymerase chain reaction (PCR) (10) was used to assay for the presence of lacZ in splenic DNA isolated from animals transplanted 5 to 12 months earlier. The lacZ gene was not detected in samples from either unirradiated or irradiated Balb/c mice that received vehicle (EBSS) (Fig. 2), whereas a strong signal was observed from both untreated ROSA26 animals and irradiated Balb/c mice that received ROSA26 BM (Fig. 2). A strong lacZ signal was also detected in animals injected with embryonic, adult, or clonally derived adult NSCs (Fig. 2). Because the behavior of NSCs derived from three clones (2H1, 4E8, and 3C6) was indistinguishable from that of bulk cultures, only results from a representative clone (2H1) and embryonic NSCs will be considered for the remainder of this report.

Fig. 2. Detection of lacZ in splenic DNA isolated from animals injected with ROSA26 NSCs by PCR. The lacZ gene was not detected in control (lane 1) or irradiated Balb/c animals injected with vehicle (lane 3). ROSA26 animals (lane 2) and Balb/c mice that received either ROSA26-derived BM (lane 4), embryonic NSCs (lane 5), adult NSCs (lane 6), or clonal adult NSC 2H1 (lane 7) produced strong amplification signals for lacZ (upper band; 374 base pairs). GAPDH was also amplified in the same reaction tube as an internal control (10) (lower band; 309 base pairs). [View Larger Version of this Image (44K GIF file)]

To test whether engrafted NSCs adopted a hematopoietic identity, we used in vitro clonogenic assays, immunocytochemistry, and flow cytometric analysis. For the clonogenic assays, cells from the BM of transplanted animals were plated in methylcellulose in the presence of defined cytokines (11). Ten to 14 days after plating, colonies founded by single hematopoietic progenitor cells were subjected to X-Gal histochemistry to detect -galactosidase activity (12), thereby identifying hematopoietic precursors of a NSC origin. None of the colonies derived from the BM of irradiated Balb/c animals injected with EBSS stained positively for -galactosidase (Fig. 3A). Conversely, BM isolated from recipients of either embryonic or adult NSCs formed colonies that reacted strongly to X-Gal (Fig. 3, B and C). A few colonies (<5%) did not stain positively for -galactosidase (Fig. 3C), showing that some endogenous hematopoietic progenitors had survived the sublethal irradiation. Different types of colonies generated from BM isolated from adult NSC recipients included pure granulocyte (13%), granulocyte-macrophage (Fig. 3, D, E, and F) (30%), and pure macrophage (Fig. 3, G, H, and I) (22%), as well as mixed colonies (19%). Megakaryocytic and B cell colonies were also present, although at lower frequencies (<1% and <10%, respectively). Erythroid cells were not taken into account in this analysis because their evaluation cannot be reliably carried out by X-Gal staining. None of the NSC cultures proliferated or formed colonies when used in the same clonogenic assay before injection. Thus, ROSA26-derived NSCs can give rise to hematopoietic precursors after engraftment into irradiated Balb/c hosts.

Fig. 3. NSCs produce early hematopoietic cells after transplantation into irradiated Balb/c recipients. An in vitro clonogenic assay (11) was used to analyze hematopoietic precursors in Balb/c mice injected with either embryonic or clonal adult NSCs, both of which yielded identical results. X-Gal histochemistry was used to identify hematopoietic clones derived from NSCs after 10 to 14 days in culture (12). Whereas none of the colonies from Balb/c BM stained positively for -galactosidase (A), colonies from the BM of animals that received adult NSCs displayed -galactosidase activity (blue) (B). In the same cultures a few unlabeled clones were found in Balb/c mice injected with clonal adult NSCs (C) (arrow), showing the persistence of a small number of endogenous (Balb/c) hematopoietic precursors in recipient animals. NSC-derived (-galactosidase-reactive) colonies were further characterized by morphology. Colonies with distinctive granulocyte-macrophage (D and E) and pure macrophage (G and H) characteristics before (D and G) and after (E and H) reaction with X-Gal are shown. The X-Gal reaction was stopped

prematurely to allow for morphological identification of individual cells within these colonies after staining. High-power microphotographs show the identifying morphology of the cells derived from the two types of colonies as stained by May-Gr?nwald-Giemsa [(F), granulocyte-macrophage; (I), pure macrophage]. Bars: (A), 40 æm; (B) and (C), 90 æm; (D), (E), (G), and (H), 40 æm; (F) and (I), 15 æm. [View Larger Version of this Image (113K GIF file)]

To further demonstrate the engraftment of NSCs into the hematopoietic system, we exploited the fact that distinct cell surface antigens are expressed by ROSA26 (H-2Kb) and Balb/c (H-2Kd) mice. We assayed cells isolated from the spleen, BM, and peripheral blood of transplanted and control animals by flow cytometry (13) using antibodies specific to H-2Kb and H-2Kd (14). Whereas no H-2Kb-positive (H-2Kb+) cells were found in animals injected with EBSS alone, numerous H-2Kb+ cells were detected in animals that received either ROSA26 BM or, more importantly, NSCs (Fig. 4A). By this approach, early experiments showed effective engraftment with between 105 and 107 NSCs per animal. With 106 NSCs per animal and 107 BM cells per animal, 100% of BM, 100% of embryonic NSCs, 70% of adult NSCs, and 63% of clonal-adult NSC recipients showed positive engraftment by flow cytometric analysis (n = 20, 20, 40, and 30 animals per group, respectively). In addition, donor-derived (H-2Kb+) cells were first detected in the peripheral blood of NSC recipients 20 to 22 weeks after injection compared with 16 to 18 weeks for ROSA26 BM recipients. After initial detection in peripheral blood, spleen cells were harvested and processed for dual-label flow cytometry (13) with antibodies to H-2Kb in combination with either antibodies to CD3e (anti-CD3e) (T lymphocytes), anti-CD19 (B lymphocytes), or anti-CD11b (myeloid cells) (15). A significant number of ROSA26-derived NSCs gave rise to B and T lymphocytes or myeloid cells after transplantation into Balb/c hosts (Fig. 4, A and B). None of the hematopoietic antigens tested was expressed by any NSCs before transplantation.

Fig. 4. Identification of differentiated hematopoietic cell types derived from ROSA26 NSCs. Hematopoietic cells from transplanted mice were processed for flow cytometry (13). (A) A significant number of H-2Kb+ cells were found in the BM, spleen, and peripheral blood of Balb/c animals injected with ROSA26 BM, and embryonic or adult clonal NSCs, but not in unirradiated Balb/c or EBSS recipients. Similarly, none of the CD3e, CD19, or CD11 immunoreactive cells identified in the spleens of control animals (Balb/c, EBSS) expressed H-2Kb. Conversely, a significant proportion of CD3e, CD19, or CD11b immunoreactive cells isolated from the spleens of ROSA26 animals as well as ROSA26 BM, embryonic, or adult clonal NSC recipients were H-2Kb+. All percentages were calculated relative to the total events gated (n = 6, ñSEM; * indicates $P < 0.05$ compared with Balb/c by analysis of variance). (B) Representative dual-label FACS plots identifies CD3e (panels 1, 4, and 7), CD19 (panels 2, 5, and 8), and CD11b (panels 3, 6, 9) immunoreactive cells (y axes) that express H-2Kb (x axes) in Balb/c animals that received EBSS (panels 1 to 3), and in ROSA26 BM (panels 4 to 6) or adult clonal NSC (panels 7 to 9) recipient animals. [View Larger Version of this Image (45K GIF file)]

Thus, NSCs isolated from the embryonic and adult murine forebrain, which generate neurons and glia, engraft into the hematopoietic system of irradiated hosts to produce a range of blood cell types. This demonstrates that the actual differentiation potential of adult NSCs, which are currently viewed as tripotent neural precursors, is much broader than expected.

We chose sublethal irradiation because it eliminates a significant fraction of the endogenous hematopoietic precursors without killing the mouse. We felt this would be necessary because NSCs would likely need more time to acquire a hematopoietic fate than a lethal dose would allow. That the repopulation of the immune system took on average 3 weeks longer, combined with a slightly weaker engraftment for NSC compared with BM recipient animals, seems to supports this idea. This extra time required suggests that NSCs undergo additional steps of fate determination, differentiation, and maturation with respect to BM cells to produce hematopoietic progeny.

It has been suggested by studies in various model systems that most somatic cell specialization may not involve irreversible genetic changes (16). The seminal demonstration of conserved genomic totipotentiality in adult somatic cells was provided in a study that describes the cloning of an adult ewe (17). Our work is complementary to these findings and suggests that the reactivation of dormant genetic programs may not require nuclear transfer or experimental modification of the genome. NSCs appear naturally endowed with the appropriate machinery required to express an otherwise silent genomic potentiality in response to an appropriate pattern of stimulation.

Given the fact that human NSCs can be continuously expanded for extended periods of time (18), the finding presented here may have implications for the treatment of a number of human disorders. If they behave similarly to their murine counterparts, human NSCs may provide a renewable, characterized source of cells that could be used in approaches aimed at hematopoietic reconstitution in various blood diseases and disorders.

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6.. NSCs were isolated from 14-day-old embryonic and adult striata of ROSA26 animals (Jackson Laboratories) as previously described (3). Cultures reported here were of early passage number (12 to 20), although

cells of later passage (30 to 35) produced identical results. Cultures were harvested 6 days after the last passage. The growth media used was as previously described (2) with epidermal growth factor(20 ng/ml) and fibroblast growth factor 2 (10 ng/ml) as mitogens.

7.. Male and female Balb/c mice 6 to 8 weeks old (Charles River) received whole-body irradiation (cobalt source) with a fractionated dose of 450/400 rads (4.5/4 Gy) separated by 4 hours. Mice were injected with 1 ? 106 NSCs or 1 ? 107 ROSA26 BM in 200 æl of Earle's buffered saline solution (EBSS; Gibco-BRL) through the tail vein 16 hours after irradiation (n = 4 independent experiments). All animal experimentation protocols were approved by the University of Calgary Animal Care Services.

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10.. The primer dropping method [H. Wong, W. D. Anderson, T. Cheng, K. T. Riabowol, Anal. Biochem. 223, 251 (1994) [Medline]] was used to amplify genomic DNA by PCR. Forty cycles of 94øC (1 min), 60øC (1 min), and 72øC (1 min) were used to amplify lacZ with the following primer pair: 5'-TTG GAG TGA CGG CAG TTA TCT GGA and 3'-TCA ACC ACC GCA CGA TAG AGA TTC. After 20 cycles, primers specific for glyceraldehyde-3-phosphate dehydrogenase (GAPDH; 5'-CGG AGT CAA CGG ATT TGG TCG TAT and 3'-AGC CTT CTC CAT GGT GGT GAA GAC) were added as an internal control.

11.. BM cells (22,500 cells/ml in Iscove's modified Dulbecco's medium and 2% heat-inactivated fetal bovine serum were added to MethoCult (Stem Cell Technologies, Vancouver, BC, Canada), supplemented with the appropriate cytokines, plated on 35-mm dishes, and incubated at 37øC in a 5% CO2 atmosphere. Cytokines used were the following: interleukin-3 (IL-3) (10 ng/ml), IL-7 (10 ng/ml), stem cell factor (50 ng/ml), erythropoietin (3 U/ml; R&D Systems), and IL-6 (10 ng/ml; Novartis).

12.. X-Gal working solution [5 mM K3F3(CN)6, 5 mM K4Fe(CN)6ú3H2O, 2 mM MgCl2 (Sigma)] and X-Gal (5-bromo-4-chloro-3-indoxyl--D-galactopyranoside; 1 mg/ml; in dimethyl sulfoxide; Molecular Probes) in phosphate-buffered saline (PBS) (pH 7.4) were added to methylcellulose cultures for 8 hours at 37øC.

13.. We used splenic cell suspensions prepared by grinding minced organ between frosted Corning slides, BM flushed from femurs using EBSS, and whole blood isolated in 20 mM EDTA. Erythrocytes were lysed with 144 mM NH4Cl and 17 mM tris-HCl (pH 7.2). Cells were rinsed with fluorescence-activated cell sorting (FACS) buffer (EBSS and 1.0% HIFBS), and 1 ? 106 cells were added to 100 æl of FACS buffer supplemented with the appropriate primary antibodies and incubated at 4øC for 30 min. After washing, secondary antibodies were added (where appropriate) and incubated at 4øC for 30 min. For biotinylated antibodies, isotype controls were used to set gates; otherwise, gates were set with cells alone. Cell viability was greater than 95%, by propidium iodide exclusion. Flow cytometric analysis was performed with a FACScan (Becton-Dickinson) with all events gated on the forward and side scatter.

14.. Clones AF6-88.5 (H-2Kb) and SF1-1.1 (H-2Kd) (PharMingen) were used.

15.. Clones 145-2c11 (CD3e), 1D3 (CD19), and M1/70 (CD11b) (PharMingen) were used.

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19.. Single- and triple-label immunocytochemistry was performed as previously described (2) with antibody to nestin, monoclonal antibody to type III -tubulin (Sigma), glial fibrillary acidic protein antisera (Incstar), and monoclonal antibody to O4 (immunoglobulin M; Boehringer Mannheim).
20.. We thank M. Dicay, L. Robertson, D. Schmidt, G. Gobbel, D. Spencer, R. Dawson, and P. Hill for technical assistance; E. Cattaneo and R. McKay for antibody to nestin; and J. Dick for critical assessment of this work. Supported by the Spinal Cord Society, Fergus Falls, MN, and by Comitato Telethon (grant A.116) to A.L.V.
10 August 1998; accepted 17 December 1998
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<P>Stem cells are found in various organs where they participate in tissue
homeostasis by replacing differentiated cells lostto physiological

turnover or injury. An investigation was performedto determine
whether stem cells are restricted to produce specificcell types,
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including myeloid and lymphoid cells as well as early hematopoietic<SUP>
</SUP>cells. Thus, neural stem cells appear to have a wider differentiation<SUP
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</SUP>potential than previously thought.</P>
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Reynolds, NeuroSpheres Limited, 3330 Hospital Drive Northwest, Calgary, AB,
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authors contributed equally to this work.

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Stem cells have been identified in adult tissues that undergo extensive cell
replacement due to physiological turnover orinjury such as the
hematopoietic, intestinal, and epidermal systems(<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF1">1</A>). Thes
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cells have been found in the central nervoussystem (CNS) (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF2">2</A>), a
tissue thought to be capable ofextremely limited self-repair. CNS

stem cells can generate thethree major cell types found in the adul
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brain: namely, astrocytes,oligodendrocytes, and neurons (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF3">3</A>). This

is consistentwith the view that the developmental potential of stem

cells isrestricted to the differentiated elements of the tissue in

whichthey reside. However, some developmental peculiarities
suggestcertain cells may be able to differentiate into cell types

thatare not of the same dermal origin (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF4">4</A>).
Hence, we soughtto determine whether neural stem cells (NSCs) could

produce hematopoieticprogeny.
<P>A bone marrow (BM) repopulation assay (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF5">5</A>) was

used to test this hypothesis. Hematopoietic stem cells from unfractionated<SUP>

</SUP>adult BM (10⁷cells per animal) or NSCs cultured from either th
e
embryonic oradult forebrain (10⁶ cells per animal) (<A

href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF6">6</A>) of
ROSA26 mice were systemicallyinjected into sublethally irradiated

Balb/c recipient animals(<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF7">7</A>).
ROSA26 animals were selected as the source of donortissue because

they are of a different immunological backgroundthan Balb/c and are

transgenic for <I>lacZ</I> (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF8">8</A>), whic
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encodesfor the <I>Escherichia coli</I> enzyme <IMG align=top
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Importantly,to eliminate possible contamination of NSCs with cells

of mesodermalorigin (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF9">9</A>), we

also injected clonally derived adultROSA26 NSCs (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F1">Fig. 1</A>).

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<STRONG>Fig. 1.</STRONG> Cloning of adult ROSA26 CNS stem cells. (<B>A</B>)

Single adult ROSA26 NSC plated in isolation in a single well (arrow). After (<B>B</B>) 1 and (<B>C</B>) 8 days, a cluster of cells formed, which was serially subcultured every 4 days to establish a continuous culture. (<B>D</B>)

All cells expressed the NSC antigen, nestin. Differentiation was induced by plating a fraction of these cells in 1% fetal bovine serum, in the absence of

growth factors. (<B>E</B>) The simultaneous detection of neurons [red; 25.3 ± 0.9% of total cell number (TCN); <I>n</I> = 6, ± SEM], astrogli
a
(blue; 71.6 ± 6.3% TCN; <I>n</I> = 6), and oligodendroglia (green; 0.9

± 0.01% TCN; <I>n</I> = 6) among the progeny of this cell indicate its

tripotentiality (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF19">19</A>).
Secondary clones of the cell displayed in (A) produced an average of 48 ±
;
3.2 (<I>n</I> = 6) cells capable of producing tertiary, tripotential clones, thereby demonstrating self-maintenance (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF2">2</A>). Data

are from clone 2H1. Bars: (A) to (C), 90 μm; (D), 60 μm; (E), 40 μm. <NOBR><A
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<P><!-- /FIG 1 --></TABLE></P>
<P>Polymerase chain reaction (PCR) (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF10">10</A>) was

used to assay for the presence of <I>lacZ</I> in splenic DNA isolated from animalstransplanted 5 to 12 months earlier. The <I>lacZ</I> gene wa
s
not detectedin samples from either unirradiated or irradiated Balb/
c
micethat received vehicle (EBSS) (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F2">Fig. 2</A>),

whereas a strongsignal was observed from both untreated ROSA26 animals and irradiatedBalb/c mice that received ROSA26 BM (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F2">Fig. 2</A>).
A
strong<I>lacZ</I> signal was also detected in animals injected with

embryonic,adult, or clonally derived adult NSCs (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F2">Fig. 2</A>).

Becausethe behavior of NSCs derived from three clones (2H1, 4E8, and3C6) was indistinguishable from that of bulk cultures, only resultsfrom a representative clone (2H1) and embryonic NSCs will be

consideredfor the remainder of this report. <A name=F2><!-- FIG 2 -
-></A><A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534/F2"><IMG
align=left hspace=10 src="cid:007001be45b1$74334e80$b0e24bc7@default"
vspace=5></A>
<HR>
<STRONG>Fig. 2.</STRONG> Detection of <I>lacZ </I>in splenic DNA isolated from

animals injected with ROSA26 NSCs by PCR. The <I>lacZ</I> gene was not detected

in control (lane 1) or irradiated Balb/c animals injected with vehicle (lane 3)
.
ROSA26 animals (lane 2) and Balb/c mice that received either ROSA26-derived BM

(lane 4), embryonic NSCs (lane 5), adult NSCs (lane 6), or clonal adult NSC 2H1

(lane 7) produced strong amplification signals for <I>lacZ </I>(upper band; 374

base pairs). GAPDH was also amplified in the same reaction tube as an internal

control (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF10">10</A>)
(lower band; 309 base pairs). <NOBR><A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534/F2">[View Larger

Version of this Image (44K GIF file)]</A></NOBR> <BR clear=all>
<HR>

<P><!-- /FIG 2 --></TABLE></P>
<P>To test whether engrafted NSCs adopted a hematopoietic identity, we used in

vitro clonogenic assays, immunocytochemistry,and flow cytometric
analysis. For the clonogenic assays, cellsfrom the BM of
transplanted animals were plated in methylcellulosein the presence

of defined cytokines (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF11">11</A>). Te
n
to 14days after plating, colonies founded by single hematopoietic

progenitorcells were subjected to X-Gal histochemistry to detect
<IMG align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-galactosidase<SUP>
</SUP>activity (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF12">12</A>),
thereby identifying hematopoietic precursorsof a NSC origin. None o
f
the colonies derived from the BM of irradiatedBalb/c animals
injected with EBSS stained positively for <IMG align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-galactosidase(<A

href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F3">Fig. 3</A>A).

Conversely, BM isolated from recipients ofeither embryonic or adult

NSCs formed colonies that reacted stronglyto X-Gal (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F3">Fig. 3</A>, B

and C). A few colonies (<5%) didnot stain positively for <IMG
align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-galactosidase (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F3">Fig. 3</A>C),

showingthat some endogenous hematopoietic progenitors had survived

thesublethal irradiation. Different types of colonies generated
fromBM isolated from adult NSC recipients included pure
granulocyte(13%), granulocyte-macrophage (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F3">Fig. 3</A>, D
,
E, and F) (30%),and pure macrophage (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F3">Fig. 3</A>, G
,
H, and I) (22%), as wellas mixed colonies (19%). Megakaryocytic and

B cell colonies werealso present, although at lower frequencies
(<1% and <10%, respectively).Erythroid cells were not taken

into account in this analysis becausetheir evaluation cannot be
reliably carried out by X-Gal staining.None of the NSC cultures
proliferated or formed colonies whenused in the same clonogenic
assay before injection. Thus, ROSA26-derivedNSCs can give rise to

hematopoietic precursors after engraftmentinto irradiated Balb/c
hosts. <A name=F3><!-- FIG 3 --></A><A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534/F3"><IMG
align=left hspace=10 src="cid:007201be45b1$74334e80$b0e24bc7@default"
vspace=5></A>
<HR>
<STRONG>Fig. 3.</STRONG> NSCs produce early hematopoietic cells after
transplantation into irradiated Balb/c recipients. An in vitro clonogenic assay

(<A href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF11">11</A>)

was used to analyze hematopoietic precursors in Balb/c mice injected with eithe
r
embryonic or clonal adult NSCs, both of which yielded identical results. X-Gal

histochemistry was used to identify hematopoietic clones derived from NSCs afte
r
10 to 14 days in culture (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF12">12</A>).
Whereas none of the colonies from Balb/c BM stained positively for <IMG
align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-galactosidase (<B>A</B>),
colonies from the BM of animals that received adult NSCs displayed <IMG
align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-galactosidase activity (blue)

(<B>B</B>). In the same cultures a few unlabeled clones were found in Balb/c
mice injected with clonal adult NSCs (<B>C</B>) (arrow), showing the persistenc
e
of a small number of endogenous (Balb/c) hematopoietic precursors in recipient

animals. NSC-derived (<IMG align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-galactosidase-reactive)
colonies were further characterized by morphology. Colonies with distinctive
granulocyte-macrophage (<B>D</B> and <B>E</B>) and pure macrophage (<B>G</B> an
d
<B>H</B>) characteristics before (D and G) and after (E and H) reaction with
X-Gal are shown. The X-Gal reaction was stopped prematurely to allow for
morphological identification of individual cells within these colonies after
staining. High-power microphotographs show the identifying morphology of the
cells derived from the two types of colonies as stained by
May-Grünwald-Giemsa [(<B>F</B>), granulocyte-macrophage; (<B>I</B>), pure

macrophage]. Bars: (A), 40 μm; (B) and (C), 90 μm; (D), (E), (G),

and (H), 40 μm; (F) and (I), 15 μm. <NOBR><A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534/F3">[View Larger

Version of this Image (113K GIF file)]</A></NOBR> <BR clear=all>
<HR>

<P><!-- /FIG 3 --></TABLE></P>
<P>To further demonstrate the engraftment of NSCs into the hematopoietic system
,
we exploited the fact that distinct cell surfaceantigens are
expressed by ROSA26 (H-2K^b) and Balb/c (H-2K^d) mice. We

assayed cells isolated from the spleen, BM, and peripheralblood of

transplanted and control animals by flow cytometry (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF13">13</A>)<SUP
>
</SUP>using antibodies specific to H-2K^b and H-2K^d (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF14">14</A>).
Whereas no H-2K^b-positive (H-2K^{b+}) cells were found in
animals injected with EBSS alone, numerousH-2K^{b+} cells

were detected in animals that received either ROSA26 BMor, more
importantly, NSCs (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F4">Fig. 4</A>A).

By this approach,early experiments showed effective engraftment wit
h
between 10⁵ and 10⁷ NSCs per animal. With 10<SUP>6
</SUP>NSCs per animal and 10⁷ BM cells per animal, 100% of BM, 100%

of embryonic NSCs, 70%of adult NSCs, and 63% of clonal-adult NSC
recipients showed positiveengraftment by flow cytometric analysis

(<I>n</I> = 20, 20, 40, and 30animals per group, respectively). In

addition, donor-derived (H-2K^{b+}) cells were first detected in the peripheral blood of NSC recipients20 to 22 weeks after injection compared with 16 to 18 weeks forROSA26 BM recipients. After initial

detection in peripheral blood,spleen cells were harvested and processed for dual-label flowcytometry (<A href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF13">13</A>) wit
h
antibodies to H-2K^b in combination with either antibodies to CD3e (anti-CD3e) (Tlymphocytes), anti-CD19 (B lymphocytes), or anti-CD11
b
(myeloidcells) (<A href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF15">15</A>). A

significant number of ROSA26-derivedNSCs gave rise to B and T lymphocytes or myeloid cells after transplantationinto Balb/c hosts

(<A href="http://www.sciencemag.org/cgi/content/full/283/5401/534#F4">Fig. 4</A>, A and B). None of the hematopoieticantigens tested was expressed by any NSCs before transplantation.<A name=F4><!-- FIG 4 --></A><A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534/F4"><IMG
align=left hspace=10 src="cid:007401be45b1$743aefa0$b0e24bc7@default"
vspace=5></A>
<HR>
<STRONG>Fig. 4.</STRONG> Identification of differentiated hematopoietic cell types derived from ROSA26 NSCs. Hematopoietic cells from transplanted mice were

processed for flow cytometry (<A href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF13">13</A>). (<B>A</B>) A significant number of H-2K^{b+} cells were found in the BM
,
spleen, and peripheral blood of Balb/c animals injected with ROSA26 BM, and embryonic or adult clonal NSCs, but not in unirradiated Balb/c or EBSS recipients. Similarly, none of the CD3e, CD19, or CD11 immunoreactive cells identified in the spleens of control animals (Balb/c, EBSS) expressed H-2K^b. Conversely, a significant proportion of CD3e, CD19, or CD11b

immunoreactive cells isolated from the spleens of ROSA26 animals as well as ROSA26 BM, embryonic, or adult clonal NSC recipients were H-2K^{b+}. Al
l
percentages were calculated relative to the total events gated (<I>n</I> = 6,

±SEM; * indicates <I>P</I> < 0.05 compared with Balb/c by analysis of

variance). (<B>B</B>) Representative dual-label FACS plots identifies CD3e (panels 1, 4, and 7), CD19 (panels 2, 5, and 8), and CD11b (panels 3, 6, 9) immunoreactive cells (<I>y</I> axes) that express H-2K^b (<I>x</I> axes) in Balb/c animals that received EBSS (panels 1 to 3), and in ROSA26 BM (panels 4 to 6) or adult clonal NSC (panels 7 to 9) recipient animals. <NOBR><A

href="http://www.sciencemag.org/cgi/content/full/283/5401/534/F4">[View Larger

Version of this Image (45K GIF file)]</A></NOBR> <BR clear=all>
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<P><!-- /FIG 4 --></TABLE></P>
<P>Thus, NSCs isolated from the embryonic and adult murine forebrain, which generate neurons and glia, engraft into the hematopoieticsystem of

irradiated hosts to produce a range of blood cell types.This demonstrates that the actual differentiation potential ofadult NSCs
,
which are currently viewed as tripotent neural precursors,is much

broader than expected.</P>
<P>We chose sublethal irradiation because it eliminates a significant fraction

of the endogenous hematopoietic precursors withoutkilling the mouse
.
We felt this would be necessary because NSCswould likely need more

time to acquire a hematopoietic fate thana lethal dose would allow.

That the repopulation of the immunesystem took on average 3 weeks

longer, combined with a slightlyweaker engraftment for NSC compared

with BM recipient animals,seems to supports this idea. This extra

time required suggeststhat NSCs undergo additional steps of fate determination, differentiation,and maturation with respect to BM cells to produce hematopoieticprogeny.</P>
<P>It has been suggested by studies in various model systems that most somatic

cell specialization may not involve irreversiblegenetic changes (<A

href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF16">16</A>). Th
e
seminal demonstration ofconserved genomic totipotentiality in adult

somatic cells wasprovided in a study that describes the cloning of

an adult ewe(<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF17">17</A>). Ou
r
work is complementary to these findings andsuggests that the reactivation of dormant genetic programs maynot require nuclear transfer or experimental modification of thegenome. NSCs appear naturally endowed with the appropriate machineryrequired to express

an otherwise silent genomic potentiality inresponse to an appropriate pattern of stimulation.</P>
<P>Given the fact that human NSCs can be continuously expanded for extended periods of time (<A
href="http://www.sciencemag.org/cgi/content/full/283/5401/534#RF18">18</A>), th

e
finding presentedhere may have implications for the treatment of a

number of humandisorders. If they behave similarly to their murine

counterparts,human NSCs may provide a renewable, characterized source of cellsthat could be used in approaches aimed at hematopoietic reconstitutionin various blood diseases and disorders.</P><!-- Footnotes --><!-- Acknowledgements --><!-- Appendices --><!-- Bibliography -->

<H3>REFERENCES AND NOTES</H3>

<OL>

<LI><A name=RF1><!-- comment for mosaic --></A>M. Loeffler and C. S. Potten

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in <I>Stem Cells</I>, C. S. Potten, Ed. (Academic Press, Cambridge, MA, 1997), pp. 1-27.

<LI><A name=RF2><!-- comment for mosaic --></A>B. A. Reynolds and S. Weiss,

<I>Science</I> <B>255</B>, 1707 (1992)<!-- MEDLINE ID="283:5401:534:1" -->

<A

href="http://www.sciencemag.org/cgi/external_ref?access_num=1553558&link_type=MED">[Medline]</A><!-- /MEDLINE -->;

A. Gritti, <I>et al</I>., <I>J. Neurosci.</I> <B>16</B>, 1091 (1996)<!-- MEDLINE ID="283:5401:534:2" --> <A

href="http://www.sciencemag.org/cgi/ijlink?linkType=ABST&journalCode=jneuro&resid=16/3/1091">[Abstract]</A><!-- /MEDLINE -->.

<LI><A name=RF3><!-- comment for mosaic --></A>S. J. Morrison, N. M. Shah,

D. J. Anderson, <I>Cell</I> <B>88</B>, 287 (1997)<!-- MEDLINE ID="283:5401:534:3" --> <A

href="http://www.sciencemag.org/cgi/external_ref?access_num=9039255&link_type=MED">[Medline]</A><!-- /MEDLINE -->;

R. D. G. McKay <I>Science </I><B>276</B>, 66 (1997).

<LI><A name=RF4><!-- comment for mosaic --></A>S. Tajbakhsh, <I>et al</I>.,

<I>Neuron</I> <B>13</B>, 813 (1994)<!-- MEDLINE ID="283:5401:534:4" --> <A

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N. L. M. Valtz, T. E. Hayes, T. Norregaard, S. Liu, R. D. G. McKay, <I>New

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<LI><A name=RF5><!-- comment for mosaic --></A>N. J. Tarbell, <I>et al</I>.

,

<I>Int. J. Radiat. Oncol. Biol. Phys.</I> <B>13</B>, 1065 (1987)<!-- MEDLINE ID="283:5401:534:6" --> <A

href="http://www.sciencemag.org/cgi/external_ref?access_num=3298176&link_type=MED">[Medline]</A><!-- /MEDLINE -->.

<LI><A name=RF6><!-- comment for mosaic --></A>NSCs were isolated from 14-day-old embryonic and adult striata of ROSA26 animals (Jackson Laboratories) as previously described (3). Cultures reported here were of

early passage number (12 to 20), although cells of later passage (30 to 35)

produced identical results. Cultures were harvested 6 days after the last

passage. The growth media used was as previously described (2) with
epidermal growth factor(20 ng/ml) and fibroblast growth factor 2 (10 ng/ml)

as mitogens.
<LI><A name=RF7><!-- comment for mosaic --></A>Male and female Balb/c mice
6
to 8 weeks old (Charles River) received whole-body irradiation (cobalt
source) with a fractionated dose of 450/400 rads (4.5/4 Gy) separated by 4

hours. Mice were injected with 1 × 10⁶NSCs or 1 ×

10⁷ ROSA26 BM in 200 μl of Earle's buffered saline solutio
n
(EBSS; Gibco-BRL) through the tail vein 16 hours after irradiation (<I>n</I
>
= 4 independent experiments). All animal experimentation protocols were
approved by the University of Calgary Animal Care Services.
<LI><A name=RF8><!-- comment for mosaic --></A>G. Friedrich and P. Sorriano
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<I>Genes Dev.</I> <B>5</B>, 1513 (1991)<!-- MEDLINE ID="283:5401:534:7" -->

<A
href="http://www.sciencemag.org/cgi/external_ref?access_num=1653172&link_ty
pe=MED">[Medline]</A><!-- /MEDLINE -->.

<LI><A name=RF9><!-- comment for mosaic --></A>P. Bartlett, <I>Proc. Natl.

Acad. Sci. U.S.A.</I> <B>79</B>, 2722 (1982)<!-- MEDLINE ID="283:5401:534:8
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F. Alliot, E. Lacain, B. Grima, B. Pessac, <I>ibid.</I> <B>88</B>, 1541
(1991)<!-- MEDLINE ID="283:5401:534:9" --> <A
href="http://www.sciencemag.org/cgi/external_ref?access_num=1996355&link_ty
pe=MED">[Medline]</A><!-- /MEDLINE -->.

<LI><A name=RF10><!-- comment for mosaic --></A>The primer dropping method
[
H. Wong, W. D. Anderson, T. Cheng, K. T. Riabowol, <I>Anal. Biochem.</I>
<B>223</B>, 251 (1994)<!-- MEDLINE ID="283:5401:534:10" --> <A
href="http://www.sciencemag.org/cgi/external_ref?access_num=7887471&link_ty
pe=MED">[Medline]</A><!-- /MEDLINE -->]
was used to amplify genomic DNA by PCR. Forty cycles of 94°C (1 min),

60°C (1 min), and 72°C (1 min) were used to amplify <I>lacZ</I> wit
h
the following primer pair: 5'-TTG GAG TGA CGG CAG TTA TCT GGA and 3'-TCA AC
C
ACC GCA CGA TAG AGA TTC. After 20 cycles, primers specific for

glyceraldehyde-3-phosphate dehydrogenase (GAPDH; 5'-CGG AGT CAA CGG ATT TGG

TCG TAT and 3'-AGC CTT CTC CAT GGT GGT GAA GAC) were added as an internal

control.
<LI><A name=RF11><!-- comment for mosaic --></A>BM cells (22,500 cells/ml i
n
Iscove's modified Dulbecco's medium and 2% heat-inactivated fetal bovine
serum were added to MethoCult (Stem Cell Technologies, Vancouver, BC,
Canada), supplemented with the appropriate cytokines, plated on 35-mm
dishes, and incubated at 37°C in a 5% CO₂ atmosphere.
Cytokines used were the following: interleukin-3 (IL-3) (10 ng/ml), IL-7 (1
0
ng/ml), stem cell factor (50 ng/ml), erythropoietin (3 U/ml; R&D
Systems), and IL-6 (10 ng/ml; Novartis).
<LI><A name=RF12><!-- comment for mosaic --></A>X-Gal working solution [5 m
M
K₃F₃(CN)₆, 5 mM
K₄Fe(CN)₆·3H₂O, 2 mM
MgCl₂ (Sigma)] and X-Gal (5-bromo-4-chloro-3-indoxyl-<IMG
align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-<FONT
size=-1>D</FONT>-galactopyranoside; 1 mg/ml; in dimethyl sulfoxide;
Molecular Probes) in phosphate-buffered saline (PBS) (pH 7.4) were added to

methylcellulose cultures for 8 hours at 37°C.
<LI><A name=RF13><!-- comment for mosaic --></A>We used splenic cell
suspensions prepared by grinding minced organ between frosted Corning
slides, BM flushed from femurs using EBSS, and whole blood isolated in 20 m
M
EDTA. Erythrocytes were lysed with 144 mM NH₄Cl and 17 mM
tris-HCl (pH 7.2). Cells were rinsed with fluorescence-activated cell
sorting (FACS) buffer (EBSS and 1.0% HIFBS), and 1 × 10⁶

cells were added to 100 µl of FACS buffer supplemented with the
appropriate primary antibodies and incubated at 4°C for 30 min. After

washing, secondary antibodies were added (where appropriate) and incubated

at 4°C for 30 min. For biotinylated antibodies, isotype controls were

used to set gates; otherwise, gates were set with cells alone. Cell
viability was greater than 95%, by propidium iodide exclusion. Flow
cytometric analysis was performed with a FACScan (Becton-Dickinson) with al
l
events gated on the forward and side scatter.
<LI><A name=RF14><!-- comment for mosaic --></A>Clones AF6-88.5
(H-2K^b) and SF1-1.1 (H-2K^d) (PharMingen) were used.

<LI><A name=RF15><!-- comment for mosaic --></A>Clones 145-2c11 (CD3e), 1D3

(CD19), and M1/70 (CD11b) (PharMingen) were used.
<LI><A name=RF16><!-- comment for mosaic --></A>M. A. Di Berardino,
<I>Genomic Potential of Differentiated Cells</I> (Columbia Univ. Press, New

York, 1997), pp. 1-3.
<LI><A name=RF17><!-- comment for mosaic --></A>I. Wilmut, A. E. Schnieke,

J. McWhir, A. J. Kind, K. H. S. Campbell, <I>Nature</I> <B>385</B>, 810
(1997)<!-- MEDLINE ID="283:5401:534:11" --> <A
href="http://www.sciencemag.org/cgi/external_ref?access_num=9039911&link_ty
pe=MED">[Medline]</A><!-- /MEDLINE -->.

<LI><A name=RF18><!-- comment for mosaic --></A>A. L. Vescovi <I>et al.</I>
,
<I>Exp. Neurol., </I>in press; J. D. Flax<I> et al.</I>, <I>Nature
Biotechnol. </I><B>16, </B>1033 (1998).
<LI><A name=RF19><!-- comment for mosaic --></A>Single- and triple-label
immunocytochemistry was performed as previously described (2) with antibody

to nestin, monoclonal antibody to type III <IMG align=top alt="beta "
src="cid:006c01be45b1$742a26c0$b0e24bc7@default">-tubulin (Sigma), glial
fibrillary acidic protein antisera (Incstar), and monoclonal antibody to O4

(immunoglobulin M; Boehringer Mannheim).
<LI><A name=RF20><!-- comment for mosaic --></A>We thank M. Dicay, L.
Robertson, D. Schmidt, G. Gobbel, D. Spencer, R. Dawson, and P. Hill for
technical assistance; E. Cattaneo and R. McKay for antibody to nestin; and

J. Dick for critical assessment of this work. Supported by the Spinal Cord

Society, Fergus Falls, MN, and by Comitato Telethon (grant A.116) to A.L.V.

</LI></OL>10 August 1998; accepted 17 December 1998 </DIV></BODY></HTML>

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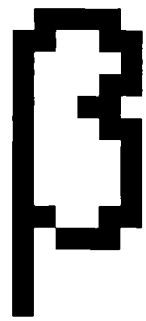

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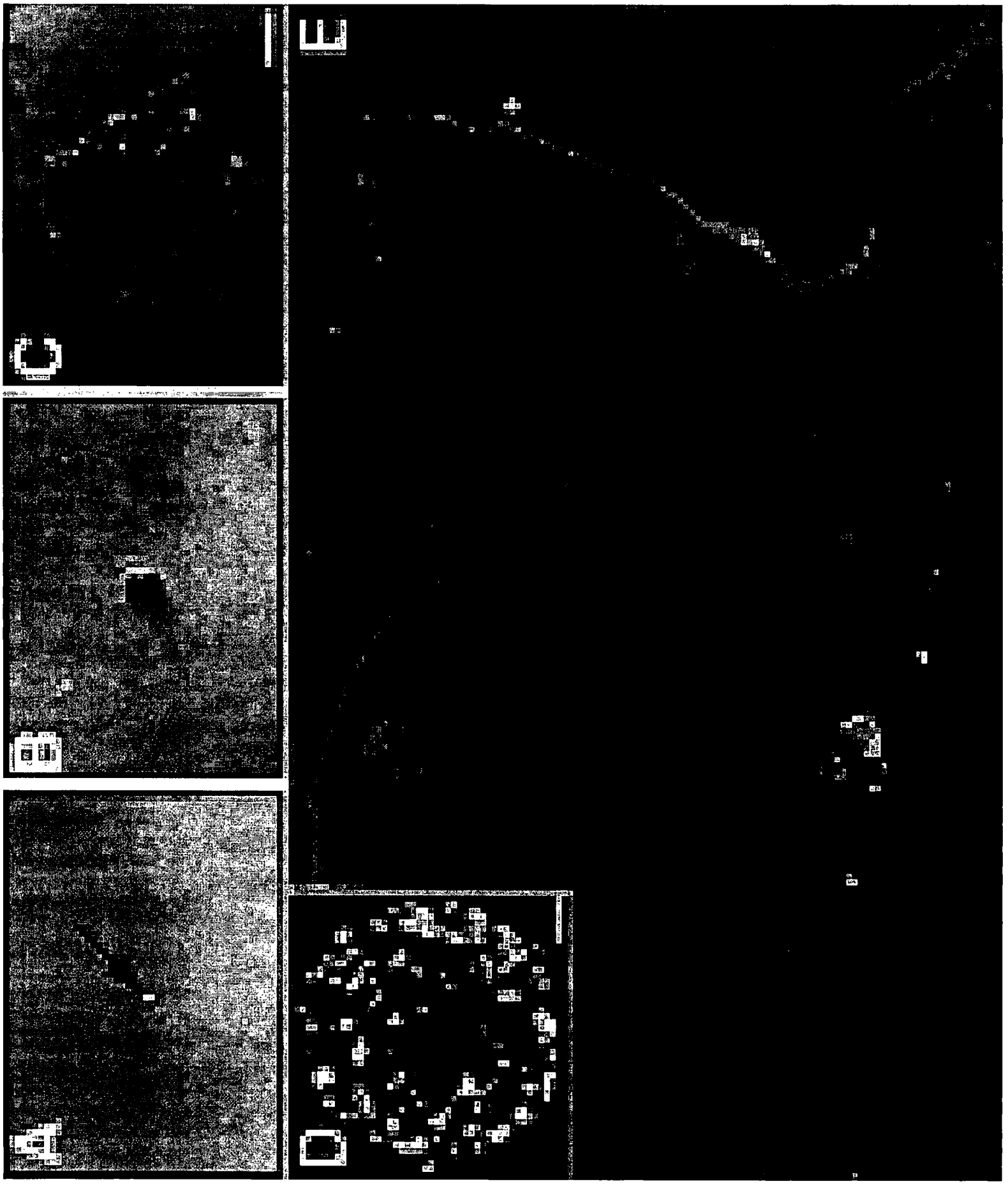

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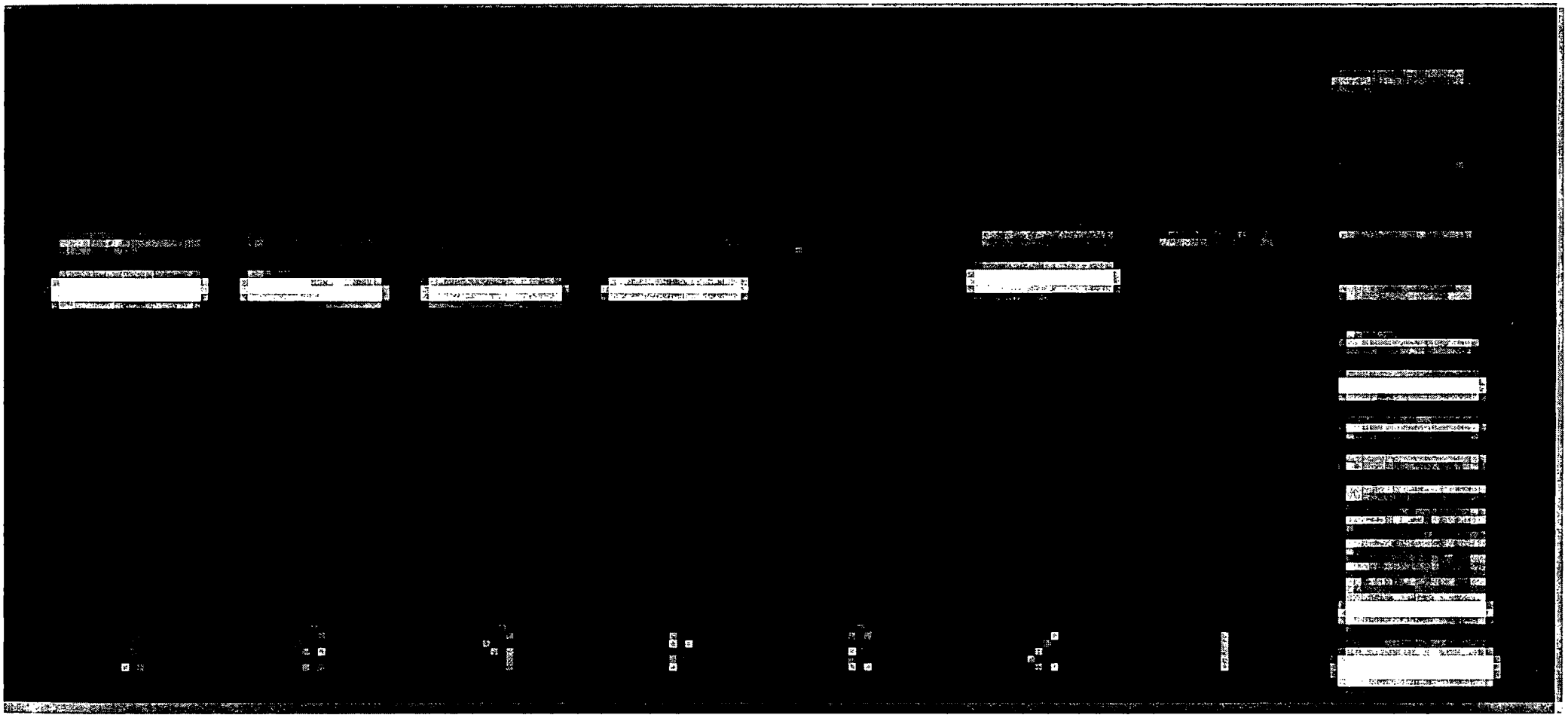

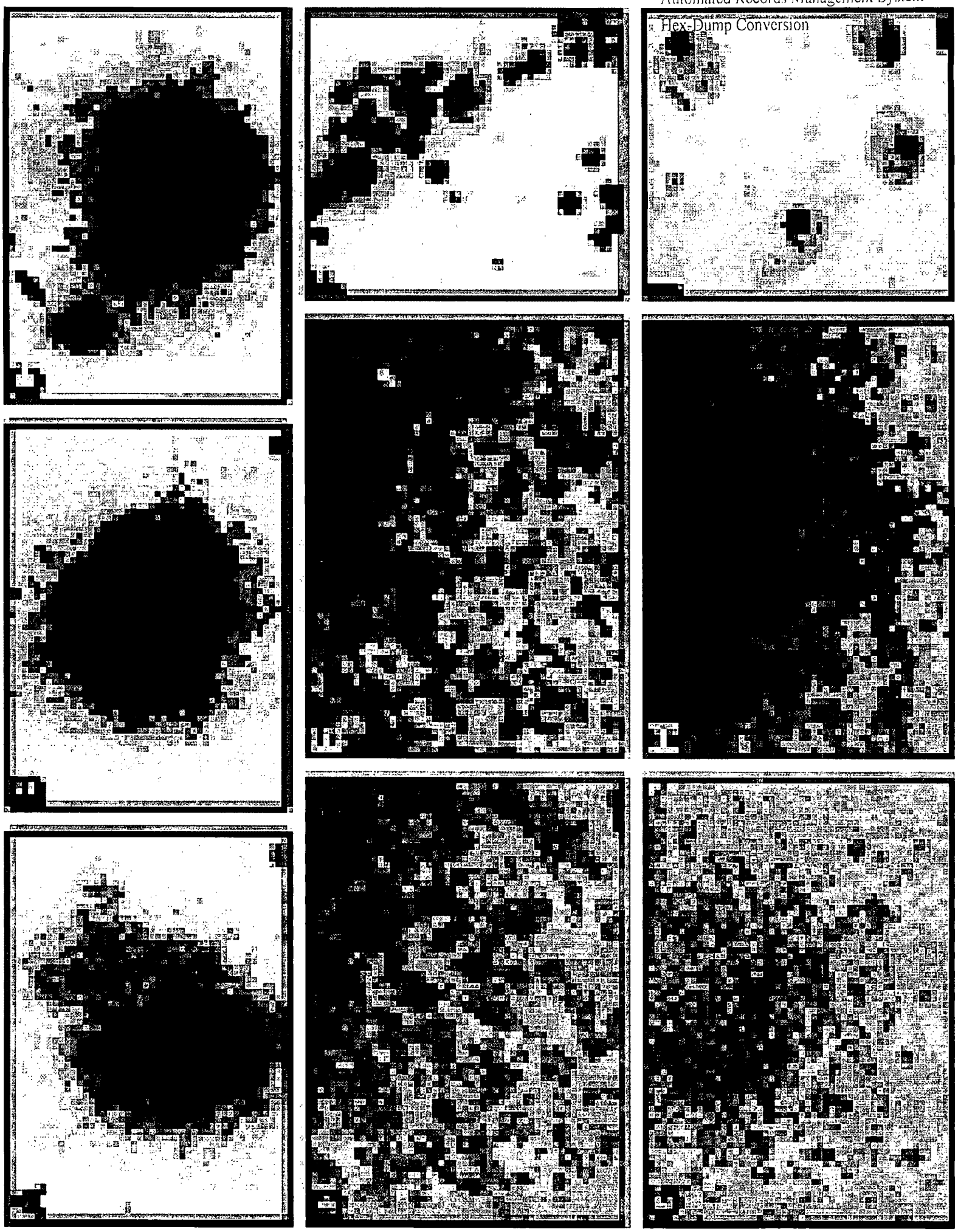
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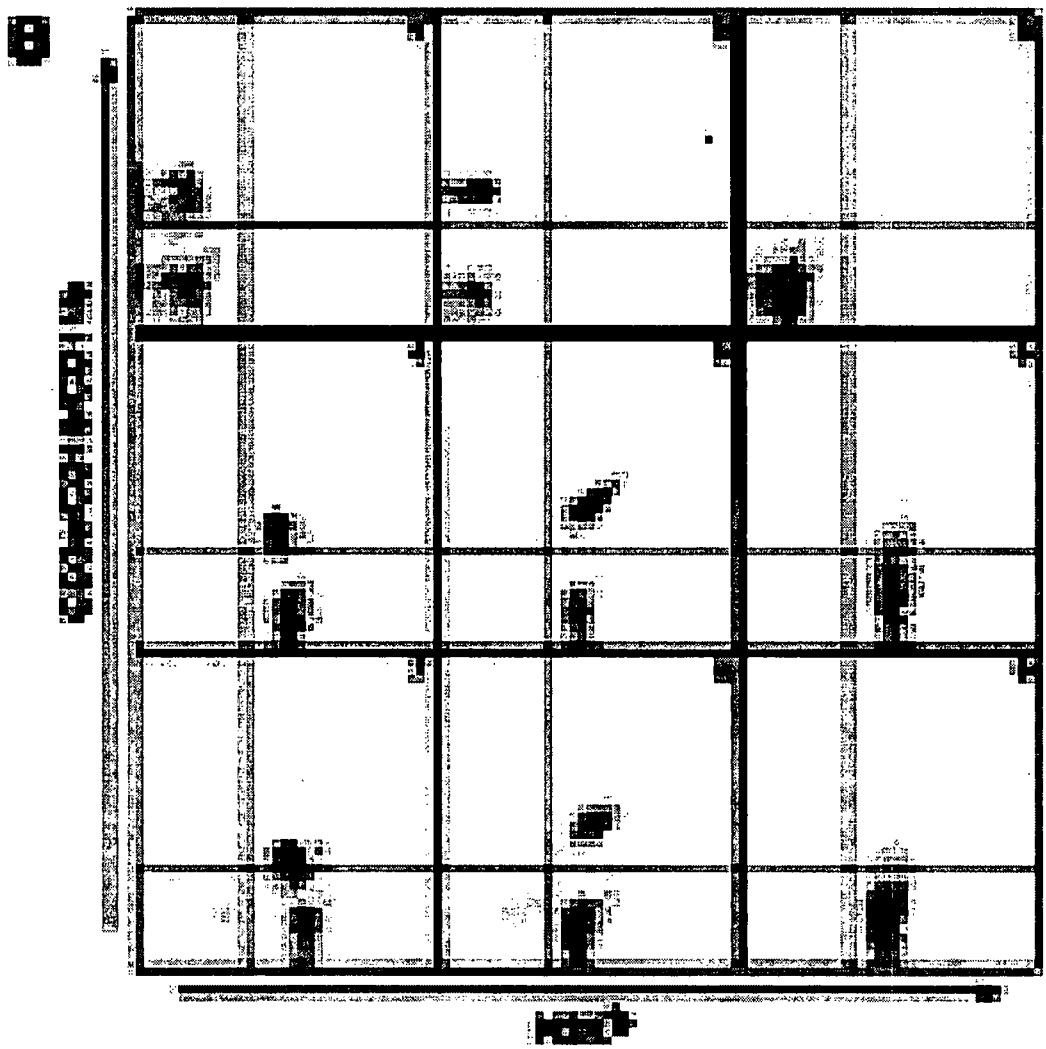

Automated Records Management System

Hex-Dump Conversion

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:23-JAN-1999 19:07:59.00

SUBJECT: stem cells - various

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 issues to address: 1) what Varmus requested of us; and 2) individual perspectives on what conclusions and recommendations we will reach.

First, because there seemed to be uncertainty, my notes on what Varmus requested were: a) within 6 weeks, ethical guidelines on funding stem cell research on presently allowable by NIH's understanding of legal advice; and b) in our report itself, recommendations on the source of ES cells in the following areas:
1. method to generate ES cells vs. to generate a human being;
2. ethical considerations for deriving ES cells by different means; and
3. distinction between totipotent cells ("embryos") derived by sexual vs. asexual means vis-a-vis their moral status.

Second, some of us concluded it would be helpful for the february meeting for commissioners to state their perspectives on ES cell research. The following are mine, categorized into cells derived from:

Aborted Fetuses: Acceptable to me under current guidelines and restrictions. Safeguards applicable to obtaining and using fetal materials should apply to use of derived ES cells. I make no distinction between spontaneously and intentionally aborted fetuses (with decision on abortion separated from decision to extract stem cells, of course). Decision to abort is a legal right of the woman.

IVF Excess Oocytes: Acceptable to me, provided ES cell research fall under the same restrictions and guidelines as those derived from aborted fetuses. Here, however, the separate decisions are between destroying the oocyte by discarding them, versus destroying them in the process of producing ES cells. Therefore, decision to discard must be made before asking women to donate oocytes for ES production. I see at least three reasons for permitting use: 1) there is a legal right by the woman (and the sperm donor?) to destroy the excess oocytes, whether or not one's moral position is that the fertilized oocyte is a fetus (if a fetus, covered by Roe v. Wade). 2) Oocytes are to be destroyed anyway, so analogous to aborted fetus situation. 3) The oocyte has no prospect of becoming a baby. Furthermore, I do not believe the fertilized oocyte has the same moral status as a more differentiated "embryo."

Creating Embryos for Research: Personally, I do not have an ethical

problem, provided safeguards are in place (e.g., the fertilized oocyte is not placed in an environment in which it could develop into a baby, or a nonviable oocyte is created). In sum, technical conditions are established to make it extremely improbable that a baby could result. However, for public policy purposes, I would not support public financing of this approach, but would prefer public funding of approaches making embryo creation unnecessary or much less preferable, such as research to establish multiple cell lines and stripping cells of their immunological liabilities. I would not prohibit private research, although my dilemma is that I would be constrained from impressing guidelines for private research, as it might be seen as supporting it. Public funding for alternatives to creating oocytes for research in the ES cell area is a greater good because it seeks stem cell research that is more widely applicable than the "customized" somatic cell nuclear transfer method would be, and would be available to more people (sooner?).

A last comment. There seem to be inconsistencies in some of the documents coming from the Administration. There are two pronouncements in our materials against creating human embryos for research (12/2/94; 3/97), but in the statement of Administration policy on S. 1601 (2/9/98), it states the Administration would "permit somatic cell nuclear transfer using human cells for the purpose of developing stem cell...technology..."

larry miike
- att1.htm========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

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<DIV><FONT color=#000000 size=2>A couple of issues to address: 1) what Varmus

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<DIV><FONT color=#000000 size=2></FONT> </DIV>
<DIV><FONT color=#000000 size=2>larry miike</FONT></DIV></BODY></HTML>

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

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "r. alta charo" <racharo@facstaff.wisc.edu> ("r. alta charo" <racharo@facstaff.wisc.edu> [UNKNOWN])

CREATION DATE/TIME:25-JAN-1999 09:51:25.00

SUBJECT: wash fax

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

TEXT:
this is a headline from wash fax; would someone who has an account please
check
it out for us? thanks!

SENATE SUBCOMMITTEE TO QUESTION ADMINISTRATION ON DECISION TO FUND STEM CELL RESEARCH
http://www.washingtonfax.com/p1/1999/19990125b.html

plus there's also this of other interest

HUMAN SUBJECTS WORKSHOP WILL TAKE UP ISSUES INVOLVING CHILDREN IN RESEARCH
http://www.washingtonfax.com/p1/1999/19990125c.html

- att1.htm========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:
<html>
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check it out for us? thanks!

SENATE SUBCOMMITTEE TO QUESTION ADMINISTRATION ON DECISION TO FUND STEM

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IN RESEARCH
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</u></html>

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

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:25-JAN-1999 10:00:32.00

SUBJECT: RE: wash fax

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

TEXT:
Commissioners:

Sen. Specter will again hold a hearing on stem cell research. The hearing is
tomorrow (Jan 26). Witnesses currently scheduled are: Harold Varmus; Harriet
Rabb; Richard Doerflinger, and me. The focus of the hearing is the NIH/DHHS
legal opinion. NBAC was asked to provide Specter with an update on its report.
My testimony is in the process of being cleared by DHHS/OMB, but I attach it
below for your information. There may still be changes--but it is intended to
be short and non-controversial.

<<Senate Testimony Jan 26.doc>>

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: r. alta charo [SMTP:racharo@facstaff.wisc.edu]
Sent: Monday, January 25, 1999 9:48 AM
To: NBAC Members E-list
Subject: wash fax

this is a headline from wash fax; would someone who has an account please check it out for us? thanks!

SENATE SUBCOMMITTEE TO QUESTION ADMINISTRATION ON DECISION TO FUND STEM
CELL RESEARCH

<http://www.washingtonfax.com/p1/1999/19990125b.html>

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<http://www.washingtonfax.com/p1/1999/19990125c.html>
- Senate Testimony Jan 26.doc========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:
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The following is a HEX DUMP:

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

[REVISED DRAFT
as of 5:45pm, Friday January 22, 1999]

Testimony of

Eric M. Meslin, Ph.D
Executive Director
National Bioethics Advisory Commission
Rockville, Maryland 20852

Before

Subcommittee on Labor, Health and Human Services,
Education and Related Agencies
Committee on Appropriations
United States Senate

January 26, 1999

Good morning Mr. Chairman, and members of the subcommittee. My name is Eric Meslin. I am the Executive Director of the National Bioethics Advisory Commission.

I was privileged to appear before your subcommittee on December 2, 1998 to offer some brief remarks on the subject of human stem cell research. At that hearing, Mr. Chairman, I informed the subcommittee that in his November 20th letter to President Clinton, the NBAC Chair, Dr. Harold Shapiro, addressed only the immediate issue of the purported experiment involving the fusion of a cow egg and a human cell, and that NBAC would devote a majority of its next meeting to the broader issue raised by President Clinton in his November 14, 1998 letter to the Commission, namely that NBAC "undertake a thorough review of the issues associated with ... human stem cell research, balancing all ethical and medical considerations".

Just this past week NBAC met for the 26th time since being established by President Clinton. The Commission devoted the entire day, January 19th, to the topic of human embryonic stem cell research, hearing testimony from a number of leading scientists, bioethicists, theologians, legal scholars, and the public.

The purpose of this meeting was to provide NBAC with a deeper understanding of the ethical, scientific, legal, medical, and policy issues that are raised by this important area of research. While the Commission did not reach any immediate conclusions--nor were they expecting to—it may be helpful to describe the range of issues that were discussed, and then to describe our timetable for completing this report.

In our view an understanding of the legal status regarding the use of federal funds to conduct human embryonic stem cell research provides an important context for fully understanding the ethical issues. At our recent meeting, NBAC was interested to learn that the Office of the General Council of the Department of Health and Human Services has rendered an opinion that the legal issue has been settled as to whether federal funds may be used for research conducted with human pluripotent stem cells derived from embryos created by *in vitro fertilization* or from primordial germ cells isolated from the tissue of non-living fetuses. We are planning to carefully review this opinion since it provides one of the many pieces of valuable information we will rely on to fully address the bioethical issues involved in this area of research.

In testimony before us, we heard some compelling arguments in favor of permitting research on human embryonic stem cells, based principally on the very promising results of previous animal studies. Several beneficial uses of these cells are anticipated, including:

- understanding basic and developmental biology;
- the development of transplantation therapies for the treatment of diseases such as Parkinson's disease and diabetes;
- the discovery of new drugs; and
- the study of infertility and birth defects.

It was also clear that a number of important scientific issues must be resolved before any actual therapies can be developed or tested in human beings. These issues include:

- how to specifically direct ES cells to differentiate into specific types, such as cardiac muscle or nerve cells;
- how to overcome the problem of immune rejection of such transplanted tissue; and
- how stem cells derived from fetal primordial germ cells (EG cells) differ from stem cells derived from embryonic sources (ES cells), and whether these differences have any functional importance.

We also heard some words of caution, and objection to all forms of research involving the human embryo, the human fetus, or the cells or tissues derived from these sources respectively. Some of these concerns related to the potential for complicity in the use of cells derived from spare or "excess" embryos. Other concerns related to more fundamental objections to the use of human fetal or embryonic material, irrespective of their source or potential for benefit.

The focus of the NBAC effort is to develop sound public policy proposals based on appropriate scientific, medical, ethical, and legal considerations. In this respect, we hope to use the experiences from former deliberative bodies including the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the DHHS Ethics Advisory Board, the Fetal Tissue Transplantation Research Panel, and the NIH Director's Embryo Research Panel. We will also be contacting a variety of public, professional, scientific and other organizations seeking their views on these issues. And, as with all NBAC reports, our deliberations, agendas, transcripts and working papers will be available on our website at www.bioethics.gov.

In reviewing a working draft outline of the report prepared by my staff, the Commission expressed an interest in developing a report that was focused on a set of answerable and timely questions, but that would also be able to anticipate certain issues. The specific questions our report will answer are now being developed for the NBAC's consideration, but they will likely include:

- Is it ethically acceptable to conduct research using human embryonic stem cells derived from fetal material?
- Is it ethically acceptable to conduct research using human embryonic stem cells obtained from existing embryos?
- Is it ethically acceptable to produce new human embryos as a source of embryonic stem cells for research?

I should note that these are questions relating to the ethics of embryonic stem cell research, not the legality of using federal funds to conduct this research. If the answer to any of these questions is yes, it would then be incumbent on NBAC to describe the conditions of oversight and review that would be necessary to permit research to proceed.

Now let me say a word about our timetable. As you know, Mr. Chairman, NBAC is subject to the Federal Advisory Committee Act (1972), and the Government in Sunshine Act (1976) which require that we conduct all of our business in public, and come to conclusions in public. This means that any Commission decisions—be they interim conclusions or final recommendations--can only occur at our NBAC meetings. We are committed to completing this report by June 1999, or thereabouts, so NBAC and it staff have mobilized to work as expeditiously as possible. Additional meetings have been scheduled—we will be meeting next week, February 2-3, in Princeton, New Jersey, and monthly thereafter. I should note, however, that the Commission is preparing for the possibility of being able to provide to the President conclusions on certain issues within the next few months. We are aware of NIH's interest in moving forward with stem cell research, and Dr. Shapiro has indicated to Dr.Varmus that if NBAC reaches any interim conclusions they will be shared with NIH and others. Naturally, Mr. Chairman, we will be pleased to provide you and your staff with an update on our work as it proceeds.

I would now be pleased to answer any questions you may have.

Attachments

List of Attachments

1. Materials from NBAC Meeting, January 19-20, 1999
- Agenda
- Table of Contents
- List of Public Testimony

2. List of Future NBAC Meetings

3. Dear colleague letter from Harold T. Shapiro, Ph.D and Eric M. Meslin, Ph.D, dated January 20, 1999

4. Letter to Harold E. Varmus, M.D, from Harold T. Shapiro, Ph.D, dated January 22, 1999

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tony Mazzaschi <Tmazzaschi@aamc.org> (Tony Mazzaschi <Tmazzaschi@aamc.org> [UNKNOWN])

CREATION DATE/TIME:26-JAN-1999 16:52:12.00

SUBJECT: Adhoc: Varmus Testimony

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
For those interested in stem cell research, the following is this morning's testimony by NIH Director Dr. Varmu's on the subject before the Senate Labor-HHS-Education Appropriations Subcommittee.

Tony Mazzaschi
AAMC

STATEMENT OF HAROLD VARMUS, M. D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BEFORE THE SENATE APPROPRIATIONS SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, EDUCATION AND RELATED AGENCIES

January 26, 1999

Mr. Chairman and Members of the Subcommittee:

I would like to thank you for the opportunity to discuss the recent decision by the Department of Health and Human Services concerning HHS funding for research utilizing human pluripotent stem cells. In testimony to this Subcommittee on December 2, 1998, I presented the exciting science of human pluripotent stem cells and described how the isolation of these cells could radically change the landscape of biomedical research. At that time, the NIH was awaiting a legal opinion from DHHS to determine whether or not the NIH could fund research utilizing these cells. The legal opinion is now available and states that research utilizing human pluripotent stem cells can be supported with Federal funds. What then are the next steps?

First, let me say that we understand and respect the different points of view that have been expressed about the important ethical and moral issues involved in this research. In developing the important safeguards that will govern funding for this research, NIH intends to consult with those representative of a broad range of views. We welcome the input of Congress as we move forward in this area.

Today, I would like to very briefly review some features of human pluripotent stem cells--how they are derived and the promises they hold for medical research and practice. I will then describe the legal opinion and the plans for the development of guidelines and oversight that will be in place before NIH would fund research with these cells. We are committed to proceeding in a careful and deliberate manner that recognizes

the ethical, societal, and scientific issues of this area of research.

I refer you to my previous testimony for a fuller description of the scientific aspects of this research. Stem cells are cells that have the ability to reproduce themselves and to give rise to other more specialized types of cells. Totipotent stem cells--such as the product of fertilization of an ovum and its progeny--are stem cells that have total potency, which means that they have the ability to form an entire mature organism, e.g., a human being, although only if placed in a woman*s uterus. In contrast, human pluripotent stem cells, which are under discussion today, do not have total potency, and hence cannot form an entire organism under any known condition. But pluripotent stem cells can give rise to all of the different types of specialized cells in the body.

The methodologies for deriving human pluripotent stem cells are not really new; pluripotent stem cells have been derived from mice since the early 1980s and, since then, from non-human primates and other animals. The first reports of deriving human pluripotent stem cells were published in November 1998 by Dr. John Gearhart and Dr. James Thomson. Neither of these investigations were supported with DHHS funds, although Dr. Gearhart*s work could have been supported with Federal funds, because he and his colleagues derived human pluripotent stem cells from primordial gonadal tissue which was taken from a non-living fetus. Federal laws and regulations already exist that govern research on fetal tissue. Dr. Thomson and his co-workers derived pluripotent stem cells from the blastocyst stage of an early embryo--the embryos used were donated by couples who were receiving infertility treatment; this derivation of stem cells from the embryo does fall under the ban on Federal funding ! in the HHS/Labor/Education Appropriations Bill. The pluripotent stem cells derived by each of these means appear to be very similar or identical in structure, function, and potential; but it will take more research to verify this.

The isolation and culturing of human pluripotent stem cells opens certain avenues of research for the first time. Let me mention just three potential applications of human pluripotent stem cells. The first is research focused on how stem cells differentiate into specific types of cells. The goal is to identify the genetic and environmental signals that direct the specialization of a stem cell to develop into specific cell types. Studying normal cell and tissue development will provide an understanding of abnormal growth and development which, in turn, could lead to the discovery of new ways to prevent and treat birth defects and even cancer.

A second and more practical application of research using these cells is in pharmaceutical development. Use of human pluripotent stem cells could allow researchers to study the beneficial and toxic effects of candidate drugs in many different cell types and potentially reduce the numbers of animal studies and human clinical trials required for drug development.

The third and most obvious potential application of these human pluripotent stem cells is to direct the specialization of the cells into cells and tissues that could be transplanted into patients for the purpose of repairing injury and pathological processes. A number of such examples

are described in my December testimony, but two are worth mentioning here.

(i) Transplantation of healthy heart muscle cells could provide new hope for patients with heart disease. The hope is to develop heart muscle cells from human pluripotent stem cells and then transplant them into the failing heart muscle in order to augment the function of the heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and integrate with the host cells. These experiments show that this type of transplantation is feasible.

(ii) In many individuals with Type I diabetes, the production of insulin in the pancreas by specialized cells called islet beta cells is disrupted. There is evidence that transplantation of either the entire pancreas or isolated islet cells could mitigate the need for insulin injections. Islet cell lines derived from human pluripotent stem cells could be used for this critical research and, ultimately, for transplantation.

Because human pluripotent stem cells continue to replicate robustly, stem cells derived from a few embryos or from a few fetuses could potentially be used in hundreds of individual research protocols.

Briefly, that is the science and the promise. We are here today to discuss the role of the Federal Government in the future of this area of research.

There are a number of advantages to using public funding for research. Perhaps the most important reason is the fact that Federal involvement creates a more open research environment-- with better exchange of ideas and data among scientists--more public engagement and more oversight. In addition, Federal support increases the fiscal resources and expands the pool of talented investigators * particularly in academia * both of which accelerate the tempo of scientific discovery.

In response to the recent announcements concerning the isolation of human pluripotent stem cells, I requested an opinion from DHHS on the legality of using DHHS funds to support or conduct research that utilizes these cells, in light of existing restrictions on human fetal tissue research and the amendment in our Appropriations bill governing human embryo research.

On January 15, 1999, DHHS delivered the following opinion. DHHS funds can be used to support research utilizing human pluripotent stem cells that are derived from human embryos: the statutory prohibition on human embryo research does not apply to research utilizing human pluripotent stem cells because human pluripotent stem cells are not embryos. The statute that bans the use of Federal funds for embryo research defines embryo as an organism derived by fertilization and other means. The statute does not, however, define organism. Therefore, the legal opinion relied on the broadly accepted science-based definition of organism: an individual constituted to carry out all life functions. By this definition--and as you heard from all the witnesses that responded to that question at your hearing on this matter on December 2, 1999--pluripotent stem cells are not

and cannot develop into organisms. Therefore, human pluripotent stem cells are not embryos and are not covered by thi!
s prohibition on Federal funding. In addition, the legal opinion states that DHHS funds can be used for research using human pluripotent stem cells that were derived from fetal tissue if the existing laws and regulations governing fetal tissue research are obeyed.

Now that the legal opinion has been rendered, what are the next steps? The approach will be careful and deliberative, recognizing the important ethical concerns that surround this area of research. I want to emphasize that NIH will not use Federal funds for research using human pluripotent stem cells until guidelines and procedures to oversee the research are developed. Let me describe the process that we have planned to ensure that any research involving human pluripotent stem cells is appropriately and carefully conducted. And as I mentioned earlier, we are interested in hearing a broad range of views.

First, all researchers currently receiving NIH support have been notified, via the NIH web site, that they cannot use DHHS funds to begin research using human pluripotent stem cells until further notice. We have made every effort to include this policy in all of our public statements. In addition, NIH program staff have been requested to notify those grantees who are most likely to have an interest in this work about this present policy. The Deputy Director for Intramural Research has also notified intramural scientists of these requirements.

Second, I will convene a subcommittee of the Advisory Committee to the Director (ACD) to develop Guidelines that specify what work using these cells can and cannot be supported with DHHS funds and outline restrictions on the use of such funds in the derivation of the cells. They will also be asked to develop an oversight mechanism to review research proposals seeking to conduct research utilizing these pluripotent stem cells. The subcommittee will meet in public session and will be composed of scientists, the lay public, ethicists, and lawyers; former members of the Human Embryo Research Panel may be asked to participate. They will be asked to consider advice from the National Bioethics Advisory Commission (NBAC), the newly established Council of Public Representatives (COPR), the public, and the Congress. NIH already has two thoughtful sets of Guidelines which will inform these efforts--the 1994 Report of the Human Embryo Research Panel and the regulations regarding Resea!
rch on Transplantation of Fetal Tissue (section 498A of the Public Health Services Act). Once developed, Guidelines for research utilizing human pluripotent stem cells will be published in the Federal Register for public comment. We hope the Guidelines and oversight process will be operational within the next several months.

In conclusion, the promise of human pluripotent stem cell research is great. And we are committed to addressing important issues surrounding this research in a deliberative and careful process to ensure that this research is conducted in an ethical, scientifically valid, and legal manner.

This concludes my statement. I would be pleased to respond to any questions you may have.

END

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tony Mazzaschi <Tmazzaschi@aamc.org> (Tony Mazzaschi <Tmazzaschi@aamc.org> [UNKNOWN])

CREATION DATE/TIME:26-JAN-1999 17:30:56.00

SUBJECT: Adhoc: NIH Position Statements on Stem Cell Research

TO: clinicalmail@aamcinfo.aamc.org (clinicalmail@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: basicmail@aamcinfo.aamc.org (basicmail@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: research-aamc@aamcinfo.aamc.org (research-aamc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: casmail@aamcinfo.aamc.org (casmail@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
NIH has issued two position statements on the conduct of research using human pluripotent stem cells derived from human fetal tissue or human embryos, one targeted to the extramural community and the other to intramural researchers. Both statements follow.

Tony Mazzaschi
AAMC

NIH POSITION ON HUMAN PLURIPOTENT STEM CELL RESEARCH

NIH funds (including equipment, facilities, and supplies purchased on currently funded grants) should not be used to conduct research using human pluripotent stem cells derived from human fetal tissue or human embryos until further notice.

Recent advances have indicated important research opportunities using human pluripotent stem cells that have been derived from fetal primordial gonadal tissue or from the inner cell mass cells of a human embryo at the blastocyst stage. While the NIH proposes to support research utilizing these human pluripotent stem cells, it will not do so until public consultation has occurred, guidelines are issued, and an oversight committee has ensured that each project is in accord with these guidelines.

Research on human stem cells derived from sources other than human embryos or fetal tissue will not be subject to these guidelines and oversight: this research will continue to be funded under existing policies and procedures.

For additional information, please consult the January 19, 1999, *Fact Sheet on Stem Cell Research* on the NIH Web site: http://www.nih.gov/news/pr/jan99/od-19.htm.

NIH POSITION ON HUMAN PLURIPOTENT STEM CELL RESEARCH

Until further notice, intramural scientists should not conduct research using human pluripotent stem cells derived from human fetal tissue or human embryos.

Recent advances have indicated important research opportunities using human pluripotent stem cells that have been derived from fetal primordial gonadal tissue or from the inner cell mass cells of a human embryo at the blastocyst stage. While the NIH proposes to support research utilizing these human pluripotent stem cells, it will not do so until public consultation has occurred, guidelines are issued, and an oversight committee has ensured that each project is in accord with these guidelines.

Research on human stem cells derived from sources other than human embryos or fetal tissue will not be subject to these guidelines and oversight: this research will continue to be funded under existing policies and procedures.

For additional information, please consult the January 19, 1999, *Fact Sheet on Stem Cell Research* on the NIH Web site: http://www.nih.gov/news/pr/jan99/od-19.htm.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Arturo Brito <abrito@peds.med.miami.edu> (Arturo Brito <abrito@peds.med.miami.edu> [UNKNOWN])

CREATION DATE/TIME:28-JAN-1999 19:45:31.00

SUBJECT: stem cell origins

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

TEXT:
Fellow commissioners,
A comment made by Dr. Varmus at our most recent meeting has had me thinking about the implications of assigning a different moral status to stem cells derived asexually vs. those derived sexually.
Should not decisions made on ethical grounds be independent of scientific possibility? Historically, ethical choices have been made on theoretical ethical constructs alone. As science advances, theories are proven or rejected. Ethically based decisions should be able to withstand scientific advancement. If scientific theories are proven inaccurate and the original ethical foundation is utilized to make a decision, is it just to modify the determination?
A good example of an application of this line of thinking is that it is currently impossible to create a human being via somatic cell nuclear transfer technique. At our January 19, 1999 meeting in Washington, D.C., Dr. Harold Varmus felt that it was ?important to distinguish between stem cells derived by sexual vs. asexual means and for us to consider whether they have the same moral status.? Suppose that we decided to consider them to indeed have separate status so that one could proceed with research that would be beneficial to living individuals. If the creation of a person were to become possible through this technique, then we would be contributing to a biased view of human clones. Unless science were to eventually prove that these new beings were in fact not human, a scenario that I have not heard anyone on this commission propose, it would be hard to justify the differential treatment of their origins.

-Just thinking

Arturo

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:28-JAN-1999 17:40:07.00

SUBJECT: NIH Policy Statement on Stem Cells

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

TEXT:
Please note that the following policy statement has been issued by NIH regarding
stem cell research. It can be found on the NIH home page at www.nih/grants/news.htm: We also have included in the briefing book which is
winging its way to all of you now, for arrival tomorrow.

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

Current News Flash(es):

NIH Position On Human Pluripotent Stem Cell Research

NIH funds (including equipment, facilities, and supplies purchased
on currently funded
grants) should not be used to conduct research using human pluripotent stem cells derived
from human fetal tissue or human embryos until further notice.

Recent advances have indicated important research opportunities
using human pluripotent stem cells
that have been derived from fetal primordial gonadal tissue or
from the inner cell mass cells of a human
embryo at the blastocyst stage. While the NIH proposes to

support
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Research on human stem cells derived from sources other than
human
embryos or fetal tissue will not
be subject to these guidelines and oversight: this research
will
continue to be funded under existing
policies and procedures.

For additional information, please consult:

Fact Sheet on Stem Cell Research", January 19, 1999.
Dr. Harold Varmus Statement On Stell Cells To Senate
Appropriations Subcommittee, Jan 26
1999.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Steve Holtzman <holtzman@mpi.com> (Steve Holtzman <holtzman@mpi.com> [UNKNOWN])

CREATION DATE/TIME:29-JAN-1999 06:25:29.00

SUBJECT: Re: stem cell origins

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

TEXT:
maybe "just" thinking arturo, but GOOD thinking!
in this case, WHY and WHAT, but not HOW, are what matter.

Arturo Brito wrote:

> Fellow commissioners,
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> differential treatment of their origins.
>
> -Just thinking
>
> Arturo

--
Steven H. Holtzman
Chief Business Officer
Millennium Pharmaceuticals, Inc.
238 Main Street
Cambridge, MA 02142
ph: 617-679-7219 fax: 617-621-0264
email: holtzman@mpi.com

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:30-JAN-1999 05:10:15.00

SUBJECT: Messages from Larry and Arturo

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

TEXT:
Thanks to Larry and Arturo for getting the groundwork set for the discussion next week in Princeton--as well as to Commissioners and staff who have kept us posted on scientific and legislative developments. I agree with Steve that Arturo has raised a good point. FYI I have attached the unedited text of my next Hastings Center Report "At Law" column (which the editor and I am in the process of shortening to fit two pages). I deal with the same issue that Arturo has flagged and tie it in with some other aspects of the present law as it relates to stem cell research and (potential) therapies.

On Larry's suggestion of a pre-statement of our views (without benefit of the oral exchange around the NBAC table): I'm largely in agreement with him.

Aborted fetuses:

I agree that this is an acceptable source for cells under current stats and regs as Larry (and Harriet Rabb, HHS gen counsel) says. I would note, however, that some could argue that current law which deals with use of fetal tissue FOR TRANSPLANTATION is inapplicable because Gearhart's method was to use fetal tissue as source of primordial germ cells for research, not transplantation. [This specific category isn't nugatory, either, since it was clear that there were special concerns--of the "let's create a baby and abort it so Grandpa's Parkinson's can be treated" variety--lay behind the statute.] Perhaps law should be expanded to cover this situation explicitly, lest argument develop that taken literally present law is inapplicable meaning either (a) feds can support research free of restrictions that apply in transplant setting, or (b) feds can't support research because it isn't of the transplantation variety.

IVF Excess Fertilized eggs:

I agree with Larry: extend the restrictions that apply to fetal tissue. Note one difficulty here: many IV-fertilized eggs do come from women who have been paid for the egg harvesting, so the fetal tissue rules may have to be modified to prohibit situation in which either the couple who "control" the IVF eggs (because they were being made and stored for that couple's planned reproduction) or the woman from whom the eggs originally came receive any ADDITIONAL financial reward for donating IVF eggs to research. I also disagree (Larry's reason #1) that Roe v. Wade has much

to say here (that is, to me, mostly a female equality decision related specifically to fetus being in body of pregnant woman). Don't think we have to argue "comparative moral status" of fertilized egg v. fetus (Larry's reason #3) although (a) it may turn out that we do, as we try to lay out our conclusions and, if so, (b) as I observe in the attached article, most people probably would regard greater protection for discarded fertilized egg/embryo over fetus as getting the moral status backwards.

Creating embryos for research:

I do not favor our arguing that such work is OK and federal restrictions ought to be removed at this time for ES cell research.

Major argument pro is that this will be best way to generate autologous tissue for transplantation (ie cloning embryo from patient's nuclear DNA). Since that work is highly speculative at this time (will scientists succeed in creating transplatable tissue using pluripotent stem cells?), I don't think we need to endorse this move and argue for removal of federal ban. (Obviously, we took no stand on this in private sector in the CLONING report, which is major reason report came under right-to-life attacks.) Second, this method--using embryos to get autologous tissue--would be obviated if work of Magli and colleagues in getting tissue-specific stem cells (there, neural stem cells) to revert to pluripotent status were to succeed. Third, Widner's new method for enhancing survival of cells transplanted to brain to treat Parkinson's disease (tested with fetal cells in mice) might have some relevance in reducing need for autologous stem cells.

Secondary argument is that scientists may need to create embryos for research because there won't be enough discarded from IVF procedures. Again, this is speculative. The extraordinary step of creating an embryo simply to use it requires either the type of argument that Varmus was testing with us (such embryos, esp. from cloning, have different moral status) OR some profound (and limited) justification based on the impossibility of carrying out highly important science (the argument that Robertson suggested, either in his terms--lesser moral status--or in terms of greater justification). That would not only require proof that this new area of science is going to pan out as glowingly as Dr. Varmus and others now predict but also a showing that the work couldn't be carried out (or would be too burdened if carried out with) private funds and without implicating those people who are strongly offended by their tax dollars going to support such work (though, if this were pressed, I'd agree with Pat King that offense to some tax payers probably does not state much of a moral argument...and no legal argument at all).

See you all next Tuesday. Be well,
Alex

****
* Alexander M. Capron acapron@law.usc.edu *
* Henry W. Bruce Professor of Law (213) 740-2557 (voice) *
* University Professor of Law and Medicine (213) 740-5502 (fax) *
* University of Southern California (213) 740-0149 (fax) *

* Los Angeles, CA 90089-0071 *
****

- INTENT.HCR========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:
Unable to convert ARMS_EXT:[ATTACH.D62]MAIL410325231.036 to ASCII,
The following is a HEX DUMP:
========== END ATTACHMENT 1 ==========

Good Intentions

Alexander Morgan Capron

Intentions, which play a central role in the law, may emerge as a major issue in debates over policy for the current hot area in biomedical research: human stem cells. If that happens, it will be only the latest twist in a story already rife with ironies, the most recent of which occurred this fall as science and the law headed in opposite directions. The story is full of convoluted legislative language, but it's worth digging into because those convolutions reveal a lot about the way public policy is shaped by strong ideologies (in this instance, warring views about abortion) and the inexorable lure of new scientific frontiers and miraculous therapies.

On 20 October 1998, Congress approved Public Law 105-277, the Omnibus Consolidated and Emergency Supplemental Appropriations (OCESA) Act. Having failed—as it has many times in the past two decades—to pass all appropriations bills prior to the beginning of Fiscal Year 1999, Congress lumped the remaining bills into a gigantic act which not only allocated funds but also specified how they could be used.

Section 511 of OCESA provides that none of the funds may be used for the creation of human embryos for research purposes or for research in which "embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero" under the Public Health Service Act and the federal regulations on human subjects research. The statute

defines an embryo as any organism "derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells" but not yet a born person or a fetus (which is defined by federal research regulations as "the product of conception from the time of implantation to removal from the uterus").

This appropriations rider continues restrictions that Congress has repeatedly imposed on NIH. The rider was first added in the wake of the 1994 report from the Human Embryo Research Panel to the Advisory Committee to the Director of NIH setting forth conditions under which certain types of research with human embryos should be permitted. On the very day the panel reported, President Clinton rejected its recommendation that federally supported scientists should be allowed to create human embryos for research purposes.

Not satisfied with an executive prohibition, Congress went a step further and forbad the use of federal funds for any research in which human embryos would die or be exposed to more than minimal risk. As specified in the rider, the risk level is keyed to the limits on the risks to which fetuses may be exposed in research. The federal regulations limit such risks to the minimum necessary to meet its own health needs or, for research not intended to benefit a fetus, not merely "minimal risk" but "the least possible risk" needed for "the development of important biomedical knowledge which cannot be obtained by other means."[i]

Barely two weeks after OCESA became law, scientists at the University of Wisconsin and Johns Hopkins University announced success in culturing human stem cells, a step that NIH Director Harold Varmus has said opens new frontiers in basic study of human development and genetic diseases, in drug and toxicity testing, and in transplantation therapy, with the prospect of creating cells to treat genetic conditions and tissues to mend damaged hearts, brains, and other organs without triggering cellular rejection.

For all the excitement generated by the scientists' announcements, it was immediately obvious that their work runs head into the ban on federal funding. Indeed, the editors of *Science*, which published the paper by James Thomson and colleagues, took the unusual step of defending their decision to disseminate this "ethically controversial research" on the ground that it complied with international human rights standards and was "legally performed even if it cannot be funded" by the government.[ii]

Support for Thomson's work came from his university and from the Geron Corp., a California biotechnology firm that expects to get an exclusive license for commercial uses of the technology. The Wisconsin team was careful to keep its stem-cell work separate from its federally supported research because its cells were derived from the inner cell mass of blastocysts grown from human eggs that had been fertilized at IVF clinics and then donated after patients had completed treatment. Thomson's achievement lies in getting the

stem cells to grow indefinitely in a lab dish while maintaining normal DNA and without becoming different types of tissue as they would as part of normal embryonic development. One of the challenges still ahead is to find the means to direct these pluripotent stems cells to differentiate into particular specialized stem cell lines (for blood, muscle, nerves, and so forth), from which tissues could be generated for transplantation.

For such grafts to succeed without triggering the process of rejection that now complicates transplantation, it will probably be necessary to develop a large bank of stem cell lines that would be compatible with the antigenic characteristics of most members of the population. The probability of tissue rejection could also be decreased if it were possible to switch off the genes that produce the antigens on the surface of these cells.

To sidestep the rejection problem entirely, an intriguing alternative would be to create a line of pluripotent stem cells matched to each transplant candidate. Therefore, considerable interest was generated by the 21 January, 1999, announcement that Ian Wilmut—Dolly's creator, who had proclaimed in 1997 that he opposed human cloning—was negotiating with several biotechnology companies, including Geron, to launch a program to clone human embryos as an alternative source of stem cells.

The Johns Hopkins group, led by John Gearhart, followed a different route, deriving their stem cells from the primordial germ

cells of fetuses aborted 5 to 9 weeks after fertilization. The possibility that these pluripotent cells may differ from those derived from blastocysts leads researchers to designate them EG (embryonic germ) rather than ES (embryonic stem) cells, but Gearhart has reported that the two seem equivalent in most regards—most important, that both give rise to cells that are "immortal," that is, capable of generating identical copies without losing their pluripotency or otherwise degrading.

The prohibitions in the NIH appropriations rider apply only to embryos but not to fetuses, so Gearhart's research could have, but did not, receive federal funding (rather, it was supported in part by the Geron Corp.). Nonetheless, on the face of it, one might reasonably suppose that research involving fetuses would be more controversial. Indeed, the first national research ethics commission had as its first, urgent assignment in 1974 to make recommendations on fetal research. The focus of its work— and of the resulting rules that are part of the federal regulations to protect human subjects—was on research with living fetus *in* and *ex utero*. But by the late 1980s, as experimental implantations of fetal tissue (for diseases such as Parkinson's) gained attention, questions arose about harvesting cells from the products of induced abortion and even about the possibility that women would become pregnant in order to produce a fetal "donor" for themselves or a relative. An NIH panel convened in March 1988 to address these concerns found that existing

regulations permitted federal support for fetal transplantation research, as did the law in most states. The panel concluded that such research would be ethical provided the abortions occur independently, with fees paid neither to the women to abort or to donate tissue nor to the abortion clinics (beyond any actual expenses) and with a prohibition on directed donation (that is, transplantation of tissue to a particular family member or friend).

Even before the panel's report was delivered in December, the Reagan Administration imposed a moratorium on the grounds that such research would encourage abortion (by associating it with a laudable goal, namely therapy) and that anyone using the products of an induced abortion was complicit in causing the death of the fetus. But with President Clinton's election the moratorium was lifted and the panel's recommendations were enacted into law.

On 15 January 1999, HHS General Counsel Harriet S. Rabb informed Dr. Varmus that federal law permits the NIH to support research conducted with human pluripotent stem cells derived by the methods developed by Drs. Thomson and Gearhart, as well as by Dr. Wilmut's method if extended to human beings. Her conclusions appear to be an unexceptionable reading of the law, assuming the scientific accuracy of the premise that pluripotent stem cells do not have the capacity possessed by totipotent cells (at the 4-cell stage) each to develop into a full human being.

Nonetheless, the general counsel's ruling reveals the puzzling

nature of the current law. First, allowing the government to fund research with human stem cells but not to fund the creation of the cells produced through IVF or cloning puts Dr. Varmus into a position like that of the shoemaker who found newly made shoes each morning in his workshop. Certainly, he can't think that elves make the stem cells while he sleeps! Yet, like the shoemaker, he's in the position that if he clothes the elves (*i.e.*, funds research to improve this methodology) his good fortune will come to an end (at least, unless Congress becomes convinced that the therapeutic promise of stem cells merits an exception to the present ban on funding).

Second, under the law federal funds may be used to derive stem cells from fetal primordial germ cells. How can one explain the willingness to allow dead fetuses to be used but not discarded IVF embryos, when in most contexts the fetus, being further developed, is more highly valued? One explanation rests on the difference in "discarding" a fetus and an embryo. In the former case, the harm comes from the abortion; the organism is dead before the research starts, even if the cells are still alive. In the latter case, the line between cellular life and organismic death is harder to conceptualize; in removing the inner cell mass from a blastocyst, scientists using the Thomson method are seen as having "destroyed [the embryo] . . . or knowingly subjected [it] to risk of ... death."

The real reason for the distinction goes beyond the degree of "complicity" that research sponsors have in the death of the early

human organism, however. In the case of fetal tissue—at least when used for transplantation—the premise of federal law is that the million-plus abortions each year offer scientists an adequate source of tissue and that abuses in the field can be prevented by outlawing both sale of fetal tissue and directed donation. With IVF embryos, these assumptions do not apply. It is not clear that the supply of "discarded" embryos would be adequate; payment to gamete-suppliers is routine; and, given the fact that no abortion is necessary to obtain the material, no assurance arises that people who provide gametes would feel moral qualms about the production of large numbers of embryos for research purposes.

The difference boils down to one of intention: lawmakers have felt that it is feasible to police against the risk that the intention to aid research will lead to the production and then abortion of fetuses but not to the production and discarding of embryos by IVF or cloning. If prospects for the great good to come from stem cell research—along with concerns about the basic process lying solely in the hands of biotechnology companies, rather than with federally supported scientists as is the norm in most other fields—prove great enough, lawmakers may revise their views about intention.

The use of embryos could be allowed with the same sort of restrictions that now exist for fetal tissue, namely, that the decision to discard them would have to be made independently of any request to use them in research and without financial inducement

to the gamete sources or the IVF or cloning clinic, donations for research purposes would only be allowed after the gamete donors had provided informed consent, and no directed donations would be allowed.

Plainly, the latter restriction could prevent what some see as an important therapeutic possibility, namely transplantation of autologous cells or tissues grown from stem cell lines based on the patient's own DNA. The recent announcement that Italian researchers had found a way to cause tissue-specific stem cells to generate other tissues suggests that it may be possible to create pluripotent stem cell lines without involving embryos. If that method, which is obviously very attractive ethically, proves inadequate, then lawmakers could be faced with a question posed recently by Dr. Varmus: Might embryos created by IVF or cloning specifically for research or therapeutic purposes be regarded as having a different moral status (in terms of their desert of protection against destruction) than embryos created for reproductive purposes?

This notion will hold no appeal for lawmakers who oppose any destruction of unborn human life. Yet for most people, the wrong that would inhere in destroying either an embryo or a fetus would depend in large part on whether such an act was done with a consent of the parents-to-be, and the willingness of the couple to initiate or agree to such an act turns on their own sense of the moral status of the embryo or fetus as weighed against competing goods. This

view would turn parental intention on its head: rather than disqualifying a donation for research, the intention to provide material for stem cell research would be the very fact that would justify treating the embryo or fetus not as an end in itself but as a means to an end.

NOTES

i. 45 Code of Federal Regulations 46.206(a)(1) & 46.208(a).

ii. Linda J. Miller and Floyd E. Bloom, "Publishing Controversial Research," *Science* 282: 1045 (6 Nov. 1998).

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:30-JAN-1999 11:51:05.00

SUBJECT: Re: Messages from Larry and Arturo

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

TEXT:
Thank you Alex for moving us along. I would add four things that I hope the Commission will discuss next week. They are assumptions that many make but that I feel we need to test.

1. I have begun talking to some IVF providers. In their experience, very few couples donate embryos they no longer need to research. Most donate to another infertile couple or choose to discard (in that order). Possibly fewer than 10 percent donate to research. So, in the view of at least 2 providers, the 10s of thousands of cryopreserved embryos currently in storage are NOT available for research. That does not mean, however, that those that would be available are insufficient. By the way, couples are not asked about donation to research until a decision has to be made about future storage, with one exception, some centers ask couples whether they want to designate what should be done with stored embryos in the event of their death, or if there is a termination of the marriage.

2. When IVF centers "form" embryos for research, they nearly always use donated gametes from sources who do not know each other. The sources have given consent to this type of research.

3. There is some question about the research "value" of cryopreserved embryos, in terms of decomposition (when stored for long periods of time).

4. The DHHS ruling does not speak to whether stem cells derived from embryos created through somatic cell nuclear transfer also may be used in research. We might assume that they can be, based on the Statement of Administration Policy that was distributed to you at the last meeting. However, because the ruling appears to be silent on this, we are seeking clarification from the DHHS Counsel.

See most of you Tuesday.

Kathi
-----Original Message-----
From: Alex Capron <acapron@law.usc.edu>
To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>

Date: Saturday, January 30, 1999 5:12 AM
Subject: Messages from Larry and Arturo

>Thanks to Larry and Arturo for getting the groundwork set for the
>discussion next week in Princeton--as well as to Commissioners and staff
>who have kept us posted on scientific and legislative developments. I
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>Note one difficulty here: many IV-fertilized eggs do come from women who
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>tissue-specific stem cells (there, neural stem cells) to revert to
>pluripotent status were to succeed. Third, Widner's new method for
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>Again, this is speculative. The extraordinary step of creating an embryo
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>of greater justification). That would not only require proof that this
>new area of science is going to pan out as glowingly as Dr. Varmus and
>others now predict but also a showing that the work couldn't be carried
>out (or would be too burdened if carried out with) private funds and
>without implicating those people who are strongly offended by their tax
>dollars going to support such work (though, if this were pressed, I'd
>agree with Pat King that offense to some tax payers probably does not
>state much of a moral argument...and no legal argument at all).
>
>See you all next Tuesday. Be well,
>Alex
>
>**
>* Alexander M. Capron acapron@law.usc.edu *
>* Henry W. Bruce Professor of Law (213) 740-2557 (voice) *
>* University Professor of Law and Medicine (213) 740-5502 (fax) *
>* University of Southern California (213) 740-0149 (fax) *
>* Los Angeles, CA 90089-0071 *
>**
>
>

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:30-JAN-1999 05:32:04.00

SUBJECT: Article for Hastings Center Report

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

TEXT:
Per the earlier e-mail: I sent the draft article I mentioned by attachment. Since I seem to recall that some Commissioners have trouble with attachments, I'm setting forth the manuscript below. Please note that parts of it may have been dropped (which the e-mail program does when it comes to a character in the WP text that it can't read). I've tried to look for trouble spots but may have missed some.
Best,
Alex

Good Intentions

Alexander Morgan Capron

Intentions, which play a central role in the law, may emerge as a major issue in debates over policy for the current hot area in biomedical research: human stem cells. If that happens, it will be only the latest twist in a story already rife with ironies, the most recent of which occurred this fall as science and the law headed in opposite directions. The story is full of convoluted legislative language, but it's worth digging into because those convolutions reveal a lot about the way public policy is shaped by strong ideologies (in this instance, warring views about abortion) and the inexorable lure of new scientific frontiers and miraculous therapies.

On 20 October 1998, Congress approved Public Law 105-277, the Omnibus Consolidated and Emergency Supplemental Appropriations (OCESA) Act. Having failed--as it has many times in the past two decades-- to pass all appropriation bills prior to the beginning of Fiscal Year 1999, Congress lumped the remaining bills into a gigantic act which not only allocated funds but also specified how they could be used.

Section 511 of OCESA provides that none of the funds may be used for the creation of human embryos for research purposes or for research in which "embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero" under the Public Health Service Act and the federal regulations on human subjects research. The statute defines an embryo as any organism "derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells" but not yet a born

person or a fetus (which is defined by federal research regulations as "the product of conception from the time of implantation to removal from the uterus").

This appropriations rider continues restrictions that Congress has repeatedly imposed on NIH. The rider was first added in the wake of the 1994 report from the Human Embryo Research Panel to the Advisory Committee to the Director of NIH setting forth conditions under which certain types of research with human embryos should be permitted. On the very day the panel reported, President Clinton rejected its recommendation that federally supported scientists should be allowed to create human embryos for research purposes.

Not satisfied with an executive prohibition, Congress went a step further and forbad the use of federal funds for any research in which human embryos would die or be exposed to more than minimal risk. As specified in the rider, the risk level is keyed to the limits on the risks to which fetuses may be exposed in research. The federal regulations limit such risks to the minimum necessary to meet its own health needs or, for research not intended to benefit a fetus, not merely "minimal risk" but "the least possible risk" needed for "the development of important biomedical knowledge which cannot be obtained by other means."

Barely two weeks after OCESA became law, scientists at the University of Wisconsin and Johns Hopkins University announced success in culturing human stem cells, a step that NIH Director Harold Varmus has said opens new frontiers in basic study of human development and genetic diseases, in drug and toxicity testing, and in transplantation therapy, with the prospect of creating cells to treat genetic conditions and tissues to mend damaged hearts, brains, and other organs without triggering cellular rejection.

For all the excitement generated by the scientists' announcements, it was immediately obvious that their work runs head into the ban on federal funding. Indeed, the editors of Science, which published the paper by James Thomson and colleagues, took the unusual step of defending their decision to disseminate this "ethically controversial research" on the ground that it complied with international human rights standards and was "legally performed even if it cannot be funded" by the government.

Support for Thomson's work came from his university and from the Geron Corp., a California biotechnology firm that expects to get an exclusive license for commercial uses of the technology. The Wisconsin team was careful to keep its stem-cell work separate from its federally supported research because its cells were derived from the inner cell mass of blastocysts grown from human eggs that had been fertilized at IVF clinics and then donated after patients had completed treatment. Thomson's achievement lies in getting the stem cells to grow indefinitely in a lab dish while maintaining normal DNA and without becoming different types of tissue as they would as part of normal embryonic development. One of the challenges still ahead is to find the means to direct these pluripotent stems cells to differentiate into particular specialized stem cell lines (for blood, muscle, nerves, and so forth), from which tissues could be generated for transplantation.

For such grafts to succeed without triggering the process of rejection that now complicates transplantation, it will probably be necessary to develop a large bank of stem cell lines that would be compatible with the antigenic characteristics of most members of the population. The probability of tissue rejection could also be decreased if it were possible to switch off the genes that produce the antigens on the surface of these cells.

To sidestep the rejection problem entirely, an intriguing alternative would be to create a line of pluripotent stem cells matched to each transplant candidate. Therefore, considerable interest was generated by the 21 January, 1999, announcement that Ian Wilmut--Dolly's creator, who had proclaimed in 1997 that he opposed human cloning--was negotiating with several biotechnology companies, including Geron, to launch a program to clone human embryos as an alternative source of stem cells.

The Johns Hopkins group, led by John Gearhart, followed a different route, deriving their stem cells from the primordial germ cells of fetuses aborted 5 to 9 weeks after fertilization. The possibility that these pluripotent cells may differ from those derived from blastocysts leads researchers to designate them EG (embryonic germ) rather than ES (embryonic stem) cells, but Gearhart has reported that the two seem equivalent in most regards--most important, that both give rise to cells that are "immortal," that is, capable of generating identical copies without losing their pluripotency or otherwise degrading.

The prohibitions in the NIH appropriations rider apply only to embryos but not to fetuses, so Gearhart's research could have, but did not, receive federal funding (rather, it was supported in part by the Geron Corp.). Nonetheless, on the face of it, one might reasonably suppose that research involving fetuses would be more controversial. Indeed, the first national research ethics commission had as its first, urgent assignment in 1974 to make recommendations on fetal research. The focus of its work--and of the resulting rules that are part of the federal regulations to protect human subjects--wason research with living fetus in and ex utero. But by the late 1980s, as experimental implantations of fetal tissue (for diseases such as Parkinson's) gained attention, questions arose about harvesting cells from the products of induced abortion and even about the possibility that women would become pregnant in order to produce a fetal "donor" for themselves or a relative. An NIH panel convened in March 1988 to address these concerns found that existing regulations permitted federal support for fetal transplantation research, as did the law in most states. The panel concluded that such research would be ethical provided the abortions occur independently, with fees paid neither to the women to abort or to donate tissue nor to the abortion clinics (beyond any actual expenses) and with a prohibition on directed donation (that is, transplantation of tissue to a particular family member or friend).

Even before the panel's report was delivered in December, the Reagan Administration imposed a moratorium on the grounds that such research would encourage abortion (by associating it with a laudable goal, namely therapy) and that anyone using the products of an induced abortion

was complicit in causing the death of the fetus. But with President Clinton's election the moratorium was lifted and the panel's recommendations were enacted into law.

On 15 January 1999, HHS General Counsel Harriet S. Rabb informed Dr. Varmus that federal law permits the NIH to support research conducted with human pluripotent stem cells derived by the methods developed by Drs. Thomson and Gearhart, as well as by Dr. Wilmut's method if extended to human beings. Her conclusions appear to be an unexceptionable reading of the law, assuming the scientific accuracy of the premise that pluripotent stem cells do not have the capacity possessed by totipotent cells (at the 4-cell stage) each to develop into a full human being.

Nonetheless, the general counsel's ruling reveals the puzzling nature of the current law. First, allowing the government to fund research with human stem cells but not to fund the creation of the cells produced through IVF or cloning puts Dr. Varmus into a position like that of the shoemaker who found newly made shoes each morning in his workshop. Certainly, he can't think that elves make the stem cells while he sleeps! Yet, like the shoemaker, he's in the position that if he clothes the elves (i.e., funds research to improve this methodology) his good fortune will come to an end (at least, unless Congress becomes convinced that the therapeutic promise of stem cells merits an exception to the present ban on funding).

Second, under the law federal funds may be used to derive stem cells from fetal primordial germ cells. How can one explain the willingness to allow dead fetuses to be used but not discarded IVF embryos, when in most contexts the fetus, being further developed, is more highly valued? One explanation rests on the difference in "discarding" a fetus and an embryo. In the former case, the harm comes from the abortion; the organism is dead before the research starts, even if the cells are still alive. In the latter case, the line between cellular life and organismic death is harder to conceptualize; in removing the inner cell mass from a blastocyst, scientists using the Thomson method are seen as having "destroyed [the embryo] . . . or knowingly subjected [it] to risk of ... death."

The real reason for the distinction goes beyond the degree of "complicity" that research sponsors have in the death of the early human organism, however. In the case of fetal tissue--at least when used for transplantation--the premise of federal law is that the million-plus abortions each year offer scientists an adequate source of tissue and that abuses in the field can be prevented by outlawing both sale of fetal tissue and directed donation. With IVF embryos, these assumptions do not apply. It is not clear that the supply of "discarded" embryos would be adequate; payment to gamete-suppliers is routine; and, given the fact that no abortion is necessary to obtain the material, no assurance arises that people who provide gametes would feel moral qualms about the production of large numbers of embryos for research purposes.

The difference boils down to one of intention: lawmakers have felt that it is feasible to police against the risk that the intention to aid research will lead to the production and then abortion of fetuses but not

to the production and discarding of embryos by IVF or cloning. If prospects for the great good to come from stem cell research--along with concerns about the basic process lying solely in the hands of biotechnology companies, rather than with federally supported scientists as is the norm in most other fields-- prove great enough, lawmakers may revise their views about intention.

The use of embryos could be allowed with the same sort of restrictions that now exist for fetal tissue, namely, that the decision to discard them would have to be made independently of any request to use them in research and without financial inducement to the gamete sources or the IVF or cloning clinic, donations for research purposes would only be allowed after the gamete donors had provided informed consent, and no directed donations would be allowed.

Plainly, the latter restriction could prevent what some see as an important therapeutic possibility, namely transplantation of autologous cells or tissues grown from stem cell lines based on the patient's own DNA. The recent announcement that Italian researchers had found a way to cause tissue-specific stem cells to generate other tissues suggests that it may be possible to create pluripotent stem cell lines without involving embryos. If that method, which is obviously very attractive ethically, proves inadequate, then lawmakers could be faced with a question posed recently by Dr. Varmus: Might embryos created by IVF or cloning specifically for research or therapeutic purposes be regarded as having a different moral status (in terms of their desert of protection against destruction) than embryos created for reproductive purposes?

This notion will hold no appeal for lawmakers who oppose any destruction of unborn human life. Yet for most people, the wrong that would inhere in destroying either an embryo or a fetus would depend in large part on whether such an act was done with a consent of the parents-to-be, and the willingness of the couple to initiate or agree to such an act turns on their own sense of the moral status of the embryo or fetus as weighed against competing goods. This view would turn parental intention on its head: rather than disqualifying a donation for research, the intention to provide material for stem cell research would be the very fact that would justify treating the embryo or fetus not as an end in itself but as a means to an end.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tim Leshan <TLESHAN@ascb.org> (Tim Leshan <TLESHAN@ascb.org> [UNKNOWN])

CREATION DATE/TIME: 5-FEB-1999 13:01:41.00

SUBJECT: Adhoc: Stem Cell Meeting

TO: Adhoc@aamcinfo.aamc.org (Adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
We'd like to take advantage of the current state of play on the issue of stem cell research by calling together some key biomedical research and patient groups to coordinate an effective strategy on potential legislation. The meeting will be held on Thursday February 11 at 3:00 PM at the Carnegie Institution of Washington, 1530 P Street, NW in the Reception Room. Please let me know if you plan to attend.

****

Tim Leshan
Director of Public Policy
American Society for Cell Biology
tleshan@ascb.org
http://www.jscpp.org/jscpp
301-530-7153 (p)
301-530-7139 (f)

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:10-FEB-1999 21:51:24.00

SUBJECT: Re: NY Times article

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

TEXT:
Regarding Arturo's thoughts, I believe we need to have a section in the "science" portion of our report which addresses Arturo's observation. Namely, how a cell's potential is inadequate vis-a-vis the ethical discussion, and that it is more relevant to discuss the necessary conditions before a cell can become a human being. Obviously, a fertilized oocyte needs to be in a proper uterine environment in order to develop into a baby. In the case of embryonic stem cells, they must be placed in a blastocyst in order to develop into a complete organism; i.e., you need to destroy another potential life (or make a chimera) in order for the stem cell to become a whole independent organism. It would be useful to describe: 1) natural fertilization, implantation and birth, gi ving the odds of reaching each stage (i.e., the number of fertilized oocytes which implant, the number which spontaneously abort, etc. for "natural" fertilization and pregnancy); 2) what needs to be done in somatic cell nuclear cloning (from our cloning report); and 3) what needs to be done to embryonic stem cells in order to create a whole, independent organism (from the description presented at the Princeton meeting).
larry

-----Original Message-----
From: Arturo Brito <abrito@peds.med.miami.edu>
To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
Date: Wednesday, February 10, 1999 3:39 PM
Subject: NY Times article

Fellow commissioners,

A few comments on the NY Times article by Gina Kolata (2/9/99):

1) The philosophical question is not, ?Where does the potential for human life lie?? It is, rather, ?How do we define a human life?? If we are only concerned about potentiality, then why not go further and state that sperm and ova deserve to be considered the moral equivalent of embryos?

2) While there are currently different opinions on the potentiality of human embryonic stem cells that we will obviously need to explore, I once again wonder about the role that current scientific possibility has in the determination of ethical construct.

3) Dr. Gearheart?s quoted ?real question?, whether stem cells by themselves could grow into a person, seems to be a rather weak argument for their special treatment. Fertilized eggs cannot by themselves grow into a person. Fertilized eggs also need a very specialized environment, one that is so complex and influential that it determines not only how the embryo will grow and develop, but also if it will at all.

-Arturo

- att1.htm========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

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<DIV><FONT color=#000000 size=2>Regarding Arturo's thoughts, I believe we need

to have a section in the "science" portion of our report which
addresses Arturo's observation. Namely, how a cell's potential is
inadequate vis-a-vis the ethical discussion, and that it is more relevant to
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order to develop into a baby. In the case of embryonic stem cells, they

must be placed in a blastocyst in order to develop into a complete organism;
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for the stem cell to become a whole independent organism. It would be
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implant, the number which spontaneously abort, etc. for "natural"
fertilization and pregnancy); 2) what needs to be done in somatic cell nuclear

cloning (from our cloning report); and 3) what needs to be done to embryonic
stem cells in order to create a whole, independent organism (from the
description presented at the Princeton meeting).</FONT></DIV>
<DIV><FONT color=#000000 size=2>larry</FONT></DIV>
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  <DIV><FONT face=Arial size=2><B>-----Original Message-----</B><BR><B>From:

  </B>Arturo Brito <<A
  href="mailto:abrito@peds.med.miami.edu">abrito@peds.med.miami.edu</A>><B
R><B>To:
```

</B>NBAC Members E-list <<A
href="mailto:nbac-members@lists.Princeton.EDU">nbac-members@lists.Princeton
.EDU</A>>
<B>Date:
</B>Wednesday, February 10, 1999 3:39 PM
<B>Subject: </B>NY Times
article

</DIV></FONT>Fellow commissioners,

A few comments on

the NY Times article by Gina Kolata (2/9/99):
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face="Times New Roman, Times">
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<DD>1) </FONT>The philosophical question is not, â€œWhere does

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<FONT face="Times New Roman, Times">
<DD>2) </FONT>While there are currently different opinions on the

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person, seems to be a rather weak argument for their special
treatment. Fertilized eggs cannot by themselves grow into a

person. Fertilized eggs also need a very specialized
environment, one that is so complex and influential that it
determines not only how the embryo will grow and develop, but also

if it will at all. </DD></DL></DL>
-Arturo
</BLOCKQUOTE></BODY></HTML>

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

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: inthenews <inthenews@SIGMAXI.ORG> (inthenews <inthenews@SIGMAXI.ORG> [UNKNOWN])

CREATION DATE/TIME:17-FEB-1999 12:31:50.00

SUBJECT: In the News

TO: SCIENCE-IN-THE-NEWS@LISTSERVER.SIGMAXI.ORG (SCIENCE-IN-THE-NEWS@LISTSERVER.SIGMAXI.ORG [UNKNOWN])
READ:UNKNOWN

TEXT:
The following roundup of science stories appearing each day in the general media is compiled by the Media Resource Service, Sigma Xi's referral service
for journalists in need of sources of scientific expertise.

IN THE NEWS

Today's Headlines - February 17, 1999

HOUSE MEMBERS PROTEST USE OF FEDERAL MONEY ON STEM CELL RESEARCH
from The New York Times

In a letter, 70 members of the House of Representatives have asked the secretary of the Department of Health and Human Services to rescind a ruling
that federal money may be used for research on human embryonic stem cells, the primordial cells from which all the tissues of the body are developed.

Human embryonic stem cells were isolated and cultivated for the first time last year in work that scientists have hailed as a first step to novel and far-reaching therapies, particularly to replace aged or damaged human tissues.

But the manner of obtaining the embryonic stem cells is viewed as morally unacceptable by opponents of abortion, including the National Conference of Catholic Bishops. The stem cells were derived by one group of biologists from long-frozen embryos that had been created in fertility clinics in excess of the patients' needs and by another group from aborted fetuses.
http://www.nytimes.com/yr/mo/day/news/national/science/sci-stem-cells.html

EX-EDITOR BLASTS AMA INTERFERENCE
from The Chicago Tribune

The former editor of the Journal of the American Medical Association said Tuesday he and his editorial staff endured constant pressure, threats and intimidation from AMA leaders, members and its lobbyists in Washington during his 17-year reign as editor of the Chicago-based medical group's prestigious journal.

In his first interview since he was fired as JAMA's editor Jan. 15, Dr. George Lundberg described an almost daily struggle to resist pressure from forces at the AMA to strip the journal of its editorial independence.
http://chicagotribune.com/business/businessnews/article/0,1051,ART-23558,00.html

H.W. KENDALL, 72, DIES; HUNTED DOWN QUARK
from The New York Times

Dr. Henry Way Kendall, one of three physicists who shared a Nobel Prize for confirming that tiny particles called quarks were the basic building blocks of matter, died on Monday while on an underwater photography shoot in Wakulla Springs State Park, south of Tallahassee, Fla. He was 72 and lived in Sharon, Mass.

The local authorities reported that Kendall, an experienced diver and underwater photographer, had joined a team from National Geographic magazine
but was working by himself before his body was found a few feet from shore. An autopsy was being performed.

Kendall was also known for his work with the Union of Concerned Scientists, an advocacy group that he helped found in 1969 and led as chairman since 1973.
http://www.nytimes.com/yr/mo/day/news/national/obit-kendall.html

FDA APPROVES NEW TEST TO DETECT LYME DISEASE
from Reuters

The Food and Drug Administration said yesterday it had approved a simple new
test for Lyme disease that can be done on the spot in a doctor's office.

The test, called PreVue and made by Chembio Diagnostic Systems of Medford, N.Y., should make it easier to diagnose the infection, which sometimes goes undetected until it has done long-lasting damage, the FDA said.

"The test provides results in an hour at the point of care, compared to the standard laboratory tests which have to be performed in a lab, delaying test
results," the FDA said in a statement. "This means doctors will be able to make a probable diagnosis quicker and start treatment with antibiotics immediately."
http://www.washingtonpost.com/wp-srv/WPlate/1999-02/17/193l-021799-idx.html

Please follow these links for more information about Sigma Xi, The Scientific Research Society:

Sigma Xi Homepage
http://www.sigmaxi.org

Media Resource Service
http://www.mediaresource.org

American Scientist magazine
http://www.sigmaxi.org/amsci/amsci.html

For feedback on In the News,
mailto:inthenews@sigmaxi.org

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:19-FEB-1999 17:29:56.00

SUBJECT: FW: AAMC Supports HHS Position on Funding Stem Cell Research (htt p://www.aamc.org/

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

TEXT:
In case you hadn't seen this. I've also included the text in the event you can't
open attachments.

We will include in your briefing books a copy of the Congressional letter to
secretary Shalala.

Eric

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

<< AAMC Supports HHS Position on Funding Stem Cell Research.htm>>

February 19, 1999

AAMC Supports HHS Position on Funding Stem Cell Research

The AAMC has joined with more than 60 patient groups and scientific organizations to send a letter to all members of Congress supporting the Department of Health and Human Services (HHS) decision that federal funding may be used to support research on human pluripotent stem cells (see Washington Highlights, Jan. 22). HHS has determined that the use of stem cells should be considered separately from the use of human embryos because pluripotent stem cells are

not
embryos as
defined by the statute and therefore should not be
subject to the current
congressional ban on federal funding of human
embryo
research.

Calling stem cell research "a tremendous avenue
... with
enormous
potential for the treatment of many diseases," the
group
letter cites the
possible implications for tissue transplantation,
drug
development and
testing, and studies of normal and abnormal cell
and
tissue growth and
development. The letter expresses support for the
National Institutes of
Health's plans "to move forward to develop clear
guidelines to address
the special scientific, legal, and ethical issues
surrounding this research."
Emphasizing "the tremendous promise this research
holds
for millions of
Americans, indeed all humankind," the letter urges
members of
Congress "to work with the NIH to ensure that this
research can move
forward with the support and oversight of the
Federal
government."

Meanwhile, 70 members of the House of
Representatives
have sent a
letter to Secretary of Health and Human Services
Donna
Shalala
objecting to the department's determination and the
decision by the
NIH to begin funding stem cell research. The
congressional letter,
dated Feb. 11, states, "Any NIH action to initiate
funding of such
research would violate both the letter and spirit
of the
federal law
banning federal support for research in which human
embryos are

harmed or destroyed." The letter takes issue with
the
HHS view as
expressed by HHS General Counsel Harriet Rabb that
the
statutory
prohibition on federal funding of human embryo
research
does not
apply to research utilizing human pluripotent stem
cells.

The congressional letter states that Ms. Rabb
"makes
significant errors
on the way to the conclusion that it would be
permissible for NIH to
fund research using stem cells harvested from human
embryos," and
urges Secretary Shalala "to correct the General
Counsel's interpretation
and to reverse Dr. Varmus's decision."
- AAMC Supports HHS Position on Funding Stem Cell Research.htm========== ATTACHMENT
1 ==========
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ition on Funding Stem Cell Research</TITLE>
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ges, Jordan J. Cohen, M.D. - President" BORDER=0 HEIGHT=53 WIDTH=171></A></TD>

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<H3><FONT FACE="Verdana, Arial, Helvetica, sans-serif">February 19, 1999</FONT>
</H3>

<BLOCKQUOTE>
<P><B><FONT FACE="Verdana, Arial, Helvetica, sans-serif">AAMC Supports
HHS Position on Funding Stem Cell Research </FONT></B></P>

<P>The AAMC has joined with more than 60 patient groups and scientific
organizations to send a letter to all members of Congress supporting the
Department of Health and Human Services (HHS) decision that federal funding
may be used to support research on human pluripotent stem cells (see <A HREF="h
ttp://www.aamc.org/advocacy/washhigh/99jan22/_1.htm"><I>Washington
Highlights</I>, Jan. 22</A>). HHS has determined that the use of stem cells
should be considered separately from the use of human embryos because pluripote
nt
stem cells are not embryos as defined by the statute and therefore should
not be subject to the current congressional ban on federal funding of human
embryo research. </P>

<P>Calling stem cell research "a tremendous avenue ... with enormous
potential for the treatment of many diseases," the group letter cites
the possible implications for tissue transplantation, drug development
and testing, and studies of normal and abnormal cell and tissue growth

and development. The letter expresses support for the National Institutes of Health's plans "to move forward to develop clear guidelines to address the special scientific, legal, and ethical issues surrounding this research." Emphasizing "the tremendous promise this research holds for millions of Americans, indeed all humankind," the letter urges members of Congress "to work with the NIH to ensure that this research can move forward with the support and oversight of the Federal government."</P>

<P>Meanwhile, 70 members of the House of Representatives have sent a letter to Secretary of Health and Human Services Donna Shalala objecting to the department's determination and the decision by the NIH to begin funding stem cell research. The congressional letter, dated Feb. 11, states, "Any

NIH action to initiate funding of such research would violate both the letter and spirit of the federal law banning federal support for research in which human embryos are harmed or destroyed." The letter takes issue with the HHS view as expressed by HHS General Counsel Harriet Rabb that the statutory prohibition on federal funding of human embryo research does not apply to research utilizing human pluripotent stem cells.</P>

<P>The congressional letter states that Ms. Rabb "makes significant errors on the way to the conclusion that it would be permissible for NIH to fund research using stem cells harvested from human embryos," and urges Secretary Shalala "to correct the General Counsel's interpretation and to reverse Dr. Varmus's decision." </P>

<P>Information: <A HREF="mailto:dbmoore@aamc.org">Dave Moore</A>, AAMC Office of Governmental Relations, 202-828-0525.</P>
</BLOCKQUOTE>
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<A HREF="/advocacy/start.htm">Advocacy</A> |
<A HREF="/newsroom/start.htm">News Room</A> |
<A HREF="/stuapps/start.htm">Student & Applicant Info.</A> |
<A HREF="/findinfo/start.htm">Information Resources</A>
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19 February 1999
<A HREF="/comments.htm">Please send us your questions and comments.
</A><A HREF="/cpyright.htm">Â© 1995-1999 AAMC</A> </FONT></I></P></CENTER>

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

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tim Leshan <TLESHAN@ascb.org> (Tim Leshan <TLESHAN@ascb.org> [UNKNOWN])

CREATION DATE/TIME:23-FEB-1999 17:28:28.00

SUBJECT: Stem Cells

TO: Sbeck@researchamerica.org (Sbeck@researchamerica.org [UNKNOWN])
READ:UNKNOWN

TO: aeckerd@prodigy.net (aeckerd@prodigy.net [UNKNOWN])
READ:UNKNOWN

TO: Jkatz@natlbcc.org (Jkatz@natlbcc.org [UNKNOWN])
READ:UNKNOWN

TO: Jsalomon@mail.faseb.org (Jsalomon@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

TO: Skoppi@endo-society.org (Skoppi@endo-society.org [UNKNOWN])
READ:UNKNOWN

TO: stomlinson@bio.org (stomlinson@bio.org [UNKNOWN])
READ:UNKNOWN

TO: EMARINCOLA@ascb.org (EMARINCOLA@ascb.org [UNKNOWN])
READ:UNKNOWN

TO: amp@amprogress.org (amp@amprogress.org [UNKNOWN])
READ:UNKNOWN

TO: KHendricks@aap.org (KHendricks@aap.org [UNKNOWN])
READ:UNKNOWN

TO: Acshipp@aamc.org (Acshipp@aamc.org [UNKNOWN])
READ:UNKNOWN

TO: mstephens@vsadc.com (mstephens@vsadc.com [UNKNOWN])
READ:UNKNOWN

TO: HarleyT@pva.org (HarleyT@pva.org [UNKNOWN])
READ:UNKNOWN

TO: sam@nhcouncil.org (sam@nhcouncil.org [UNKNOWN])
READ:UNKNOWN

TO: lsoler@jdfcure.org (lsoler@jdfcure.org [UNKNOWN])
READ:UNKNOWN

TO: ichow@faseb.org (ichow@faseb.org [UNKNOWN])
READ:UNKNOWN

TO: md@capitolassociates.com (md@capitolassociates.com [UNKNOWN])
READ:UNKNOWN

TO: stipton@ascm.org (stipton@ascm.org [UNKNOWN])
READ:UNKNOWN

TO: slrbc@aol.com (slrbc@aol.com [UNKNOWN])
READ:UNKNOWN

TO: susan_quantius@aau.edu (susan_quantius@aau.edu [UNKNOWN])
READ:UNKNOWN

TO: Dbmoore@aamc.org (Dbmoore@aamc.org [UNKNOWN])
READ:UNKNOWN

TO: fpwhite@mail.faseb.org (fpwhite@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: nwells@vsadc.com (nwells@vsadc.com [UNKNOWN])
READ:UNKNOWN

CC: tlawless@faseb.org (tlawless@faseb.org [UNKNOWN])
READ:UNKNOWN

CC: bernstei@mail.faseb.org (bernstei@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: araanan@aps.faseb.org (araanan@aps.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: rokelley@uic.edu (rokelley@uic.edu [UNKNOWN])
READ:UNKNOWN

CC: nbradish@bio.org (nbradish@bio.org [UNKNOWN])
READ:UNKNOWN

CC: pfarnham@asbmb.faseb.org (pfarnham@asbmb.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: Priscilla_Short@ama-assn.org (Priscilla_Short@ama-assn.org [UNKNOWN])
READ:UNKNOWN

TEXT:
Here is what I know on the Stem Cell issue to date. Since last we met there have been letters from the House and the Senate calling into question the HHS ruling allowing for federal funds to be used for research on derivative stem cells. I believe this moves us into a defensive position where we must work to keep stem cells out of the current embryo research ban.

The Department of Health and Human Services is drafting a response to both the House and Senate letters. HHS will not back down from the ruling, but will attempt to answer the questions raised. Shalala and Varmus testified before Specter this morning on the budget, but stem

cells came up several times. Shalala reiterated her support for the ruling and said she thinks "we are with in the law." Specter said there would be yet another hearing on this issue based on the recent letters from the Hill. He also asked each NIH institute director to provide him with information about how stem cells could be used from their perspective. It was interesting that Senator Kyl, R-AZ who signed the Senate letter to Shalala said he would submit written questions to Dr. Varmus to clarify some questions on stem cells, but asked none at the hearing.

I have spoken with Rep. Lowey's office and was told that Lowey is clearly geared up to help fend off an effort to put stem cells in the embryo ban, but she won't have much time as you might imagine.

I spoke to the Labor-HHS Subcommittee staff who said they don't know how Porter will handle the stem cell issue at this weeks Appropriations hearing where it is bound to come up. I urged them to have Porter ask a positive question before Reps Dickey or Whicker go negative. We'll have to wait and see.

Rep. Bonilla's staff tells me that he supports stem cell research, he opposed the House letter and he voted against the earlier Dickey amendment. Bonilla will be an important ally on the leadership side of the aisle.

Congressman Obey's staff urged us to work with the full Appropriations Committee because they think that may be where the battle is fought. It appears Obey will be supportive of research, but is looking for a compromise.

The fight has begun and Members are looking for our help on this one. I am sure the AAMC letter that most groups signed on to will be a big help, but there needs to be more discussions with Hill staff. I have tried to see when the Senate staff could meet again on this issue, but they did not have a date yet. Please let me know if you have any more information or questions. Thanks.

****

Tim Leshan
Director of Public Policy
American Society for Cell Biology
tleshan@ascb.org
www.jscpp.org/jscpp
301-530-7153 (p)
301-530-7139 (f)

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME: 8-MAR-1999 02:20:22.00

SUBJECT: Prof. Charo and Her Recusal From Stem Cell Discussions

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

TEXT:
I wanted to share with commissioners and NBAC staff the communication I received
from the DHHS Ethics Office regarding Alta's recusal from discussions about the
stem cell issue. Please read this carefully. If you have any questions, please
direct them to me, and I will be pleased to answer them to the best of my ability.

Eric

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: Rick Thomas [SMTP:rthomas@os.dhhs.gov]
Sent: Tuesday, March 02, 1999 8:32 AM
To: Meslin, Eric (OD)
Cc: Edgar M. Swindell
Subject: RE: ...no subject...

As for Dr. Charo, if she does not have a waiver permitting her to participate in the stem cell matter, she remains disqualified completely from all deliberations, discussions, advice, assistance, etc., on the matter. This includes formal and informal discussions not only with Commission members, but with any federal employee involved (including yourself, NBAC staff and any other employees of HHS or any other agency involved). We have encountered situations recently where individuals disqualified themselves incompletely from a matter, for example by refraining from certain formal decisions on a matter but not from all internal discussions; the failure to recuse oneself completely from all participation in a matter can lead to public criticism, Congressional

oversight, and a criminal investigation by the Inspector General, all of which actually did occur in a very recent case involving an NIH employee who appeared to have recused himself from actually voting on a matter but nevertheless still participated in internal discussions of the matter.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: David Moore <Dbmoore@aamc.org> (David Moore <Dbmoore@aamc.org> [UNKNOWN])

CREATION DATE/TIME:12-FEB-1999 17:14:55.00

SUBJECT: Adhoc: Stem Cell Letter

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
To: Organizations Interested in Medical Research

Note: This notice has been sent to the Ad Hoc Group for Medical Research Funding list serve. The Ad Hoc Group has taken no position on this issue, and use of this list serve does not imply a position on this issue.

We are still seeking endorsements for the following letter to all members of the House and Senate supporting the administration's decision on stem cell research. The deadline for signing this letter has been extended to the close-of-business on Thursday, February 18. If your organization wishes
to sign this letter, please e-mail me at <dbmoore@aamc.org>.

Dave Moore
Associate Vice President
Office of Governmental Relations
Association of American Medical Colleges
202-828-0525
FAX 202-862-6218
dbmoore@aamc.org

****

The Honorable _____
United States Senate
Washington D.C. 20510

Dear Senator _____:

The undersigned organizations applaud the determination by the Department of Health and Human Services that current law permits the use of federal funds to support research utilizing human pluripotent stem cells.

Human pluripotent stem cells have the ability to reproduce themselves indefinitely and to give rise to other more specialized types of cells, such
as muscle, skin, nerve, pancreas or blood cells. This ability to produce specialized cells opens a tremendous avenue of research with enormous potential for the treatment of many diseases. For example, human stem cells
could be used to produce different kinds of specialized cells and tissues

for use in transplantation to treat many diseases and conditions, including neurological disorders such as Parkinson*s and Alzheimer*s diseases, heart disease and stroke, diabetes, osteoarthritis, rheumatoid arthritis, and spinal cord injury.
Stem cell research also offers great promise for use in drug development and testing, to evaluate and understand both the beneficial and toxic effects of drugs on different human cell types, thus potentially reducing the need for animal studies and enabling fewer and more sharply focused human clinical trials. Research on human stem cells will open exciting new pathways by which to strengthen our understanding of normal human cell and tissue development. This, in turn, will accelerate our insights into the mechanisms of abnormal growth and development, and could lead to the discovery of radically new approaches to the prevention and treatment of birth defects and cancer.

It is essential that the Federal government play a primary role in funding and overseeing the conduct of this research so that the talent and creativity of all our scientists -- both privately and federally funded -- can be applied to this important line of research. Federal involvement creates a more open research environment, promoting the free exchange of ideas and data among scientists, and ensuring greater public engagement and the protections of federal regulatory oversight. Federal support will also increase fiscal resources and expand the pool of well-trained investigators engaged in this area of research, both of which will speed the pace of scientific discovery.

We concur with the National Institutes of Health*s plans to move forward to develop clear guidelines to address the special scientific, legal, and ethical issues surrounding this research. We are confidant that this process will have appropriate public input, as well as the advice of the National Bioethics Advisory Commission and NIH*s newly established Council of Public Representatives. NIH has made clear that it will not support any research using human pluripotent stem cells until the appropriate guidelines
have been developed and disseminated and an oversight process is in place.

Given the tremendous promise this research holds for millions of Americans, indeed all humankind, we strongly urge you to work with the NIH to ensure that this research can move forward with the support and oversight of the Federal government.

Sincerely,

Alliance for Aging Research
American Academy of Allergy, Asthma and Immunology
American Academy of Orthopaedic Surgeons
American Academy of Otolaryngology - Head and Neck Surgery
American Association for Cancer Research
American Association of Colleges of Pharmacy
American Association of Immunologists
American Association for the Study of Liver Diseases
American Heart Association
American Lung Association
American Pediatric Society

American Society for Biochemistry and Molecular Biology
American Society for Cell Biology
American Society for Microbiology
American Society for Pharmacology and Experimental Therapeutics
American Society of Hematology
American Society of Tropical Medicine and Hygiene
American Thoracic Society
American Veterinary Medical Association
Association of Academic Departments of Otolaryngology - Head and Neck Surgery
Association of American Medical Colleges
Association of Medical School Microbiology and Immunology Chairs
Association of Medical School Pediatric Department Chairs
Association of Professors of Dermatology
Citizens for Public Action
Cooley's Anemia Foundation
Cystic Fibrosis Foundation
East Carolina University School of Medicine
Federation of American Societies for Experimental Biology
Fred Hutchinson Cancer Research Center
Jeffrey Modell Foundation
Johns Hopkins University
Joint Council of Allergy, Asthma and Immunology
Juvenile Diabetes Foundation International
Krasnow Institute for Advanced Studies
Massachusetts Institute of Technology
National Alliance for Eye and Vision Research
National Alliance for the Mentally Ill
National Health Council
National Organization for Rare Disorders
National Spinal Cord Injury Association
Research!America
RESOLVE, the National Infertility Association
Society for Pediatric Research
The Genome Action Coalition

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:30-MAR-1999 16:45:42.00

SUBJECT: FW: stem cell questions

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

TEXT:
Dear Commissioners et al.

Below you'll find two documents coming from NIH regarding stem cell research.
The first is a set of one-page descriptions of benefits from stem cell research,
prepared by many NIH institutes which, according to this email, are in response
to Senator Spector's inquiries.

The second is a notice of a working group meeting being convened by Harold Varmus' Advisory Committee to the Director. This working group is part of the
process NIH is going through to develop their stem cell guidelines. I will be
attending this meeting to give an update on NBAC's work. You should know that
NIH read and may distribute to this working group the "NBAC Staff Draft Points
to Consider" document that we briefly discussed at the last NBAC meeting. They
are aware that this is a staff draft, has not been endorsed or approved by the
commission, and may change (or even disappear).

FYI, the AAAS is also meeting next week to discuss stem cells. We'll give you
an update on both meetings in Charlottesville.

Eric

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: Quinlan, Margaret (OD)
Sent: Tuesday, March 30, 1999 2:06 PM
To: Andy; Catherine; Debra; Eiseman, Elisa; Elisa; Emily; Eric;
Evadne;
Hanna, Kathi; Jody; Kathi; Kinner, J. Kyle; Lisa; Lori; Melissa; Melissa2;
Pat;
Randy; Rob; Rosemary; Sara; Sara2; Sean; Sherrie
Subject: FW: stem cell questions
Importance: High

FYI

-----Original Message-----
From: Flamberg, Gemma (OD)
Sent: Tuesday, March 30, 1999 10:57 AM
To: OD-OLPA-Leg Contacts
Subject: FW: stem cell questions
Importance: High

FYI ---

-----Original Message-----
From: Skirboll, Lana (OD)
Sent: Tuesday, March 30, 1999 10:53 AM
To: NIH Planning and Evaluation Officers
Subject: stem cell questions
Importance: High

I thought you might like to see the full package of answers to the Specter question on stem cells that went to the department. Thank you for your effort
on this and please thank everyone in your IC that put the "pedal to the metal"
to get these done in a timely fashion. please share them with your Director, if
you think he/she would be interested. We will not be sending them separately to
the Directors.

<<stemcellinsert.wpd>>

<<FRnoticeFNL.wpd>>

[Meslin, Eric]

(Billing Code 4140-01-P)
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Notice of Meeting of the Working Group to Advise the ACD on Guidelines and Oversight Process for Research Involving Human Pluripotent Stem Cells

Notice is hereby given that the Working Group of the Advisory Committee to the Director (ACD), NIH to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells, will meet in public session at the Bethesda Marriott, 5151 Pooks Hill Road, Bethesda, Maryland 20814, on April 8, 1999. The meeting will begin at approximately 9:00 a.m. and end at approximately 5:30 p.m.

The goal of the Working Group is to provide advice to the ACD about the scientific, ethical, legal, and social issues relevant to guidelines for the conduct of research utilizing human pluripotent stem cells (cells that can form most of the cells and tissues of the body) and to consider oversight options for this research.

A limited amount of meeting time will be allotted for public testimony. Individuals who wish to give five minute public testimony may sign up at the meeting site the morning of the meeting on a first come, first served basis.
Written testimony may be submitted to: the Office of Science Policy, Bldg. 1, Room 218, NIH, 9000 Rockville Pike, Bethesda, 20892.

Attendance may be limited to seat availability.

Dated:

_____
Ruth L. Kirschstein, M.D.

Deputy Director, NIH
- stemcellinsert.wpd - FRnoticeFNL.wpd========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:
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========== END ATTACHMENT 2 ==========

National Cancer Institute

In cancer research several applications of human pluripotent stem cell research will have importance. First, pluripotent stem cells may be applied to reduce the tissue toxicity brought on by cancer therapy. Already bone marrow stem cells, representing a more committed stem cell, are used to rescue 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 pluripotent stem cells would return the complete repertoire of immune response to patients undergoing bone marrow transplantation. This is important since our future plans are to manipulate the immune system after high dose chemotherapy, so that they specifically recognize cancer cells. Without a vigorous reconstituted immune system, this form of immune/vaccine therapy will not work. Other organs may benefit by replenishing their stem cell pools: injection of such pluripotent stem cells into the heart may permanently reverse cardiomyopathy caused by certain chemotherapeutic agents. It may also be possible to restore brain function after cancer treatment by injection of pluripotent stem cells that have been differentiated into neural cells.

Second, it is thought that cancer cells have certain stem cell properties; specifically, the ability to renew themselves. The isolation and characterization of stem cells and in depth study of their molecular and cellular biology may provide key secrets as to why cancer cells survive despite some very aggressive treatments. Once understood, scientists can then plot directed attacks towards the cancer "stem cell" function.

Third, there are applications in the field of gene therapy, where an understanding of stem cells would allow us to achieve long-term expression of a desired gene. In gene therapy, a DNA gene that provides a missing or necessary protein is introduced into an organ for a therapeutic effect. For successful gene therapy of an organ, it is critical that the desired gene be introduced into organ stem cells in order to achieve sufficient long-term expression and therapeutic effect. One of the biggest problems of gene therapy in clinical trials to date, has been the loss of expression (or insufficient expression), due in part to our inability to identify stem cells. The pluripotent stem cell is clearly a more versatile target cell for gene therapy since it can be manipulated to become theoretically any tissue. Thus, a single gene transfer into a pluripotent stem cell will enable scientists to generate stem cells for blood, skin, liver, or even brain targets. Moreover, pluripotent stem cells are potentially a more optimal target than a more differentiated tissue stem cell, in that they may express the transgene longer. The applications to cancer may be to engineer replacement cells that are resistant to chemotherapeutic assault, or express antibodies against cancer targets. In this latter example, the stem cell would function as a long-term delivery system for cancer therapeutics.

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) believes that human pluripotent stem cell research can develop exceptional new tools to address many important public health problems. The broadest potential application of stem cell research is the generation of cells and tissues that could be used as therapies. If scientists can learn how to control stem cell conversion into new, functionally mature cells, then physicians might be able to cure many cardiovascular diseases for which therapy is currently inadequate. For example, stem cells could potentially be used to repair the failing heart when it can no longer pump, to generate growth of heart chambers when infants are born with malformed hearts, to prevent rejection of transplanted hearts, and to repair vascular damage resulting from high blood pressure and atherosclerosis. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and work together with the host cells. These experiments show that stem cell transplantation is feasible. Stem cell research could also have ramifications for lung disorders and could lead to methods to correct defects in lung development or promote tissue repair following injury to the lung.

National Institute of Dental and Craniofacial Research

Pluripotent human stem cells offer an important new tool and resource in biomedical research. Research using animal pluripotent stem cells is already helping to improve our understanding of the complex events of tissue development and regeneration. In addition, it is providing new approaches for the development and testing of new drugs and therapies and is contributing to the development of new technologies for the repair and replacement of organs, which have been damaged by disease or injury.

This is but a glimpse of what promises to become a rapidly expanding research portfolio at NIDCR. Stem cell research should better allow us to understand the biology of inherited craniofacial anomalies such as cleft lip and cleft palate and also the way normal cells can become malignant in orofacial and pharyngeal cancer. This should provide new information to prevent and treat these diseases. In addition, stem cell research could lead to the engineering of specialized cells such as bone, cartilage and salivary cells, which can be used as replacement for organs damaged by disease or injury. Examples include the treatment of temporomandibular joint disorders (TMDs), the replacement of skeletal elements lacking or damaged in diseases such as fibrous dysplasia of bone using cells grown in special natural or synthetic scaffolding materials, and the replacement of salivary cells damaged by disease (Sjögren's Syndrome) or radiation for head and neck cancer.

National Institute of Diabetes and Digestive and Kidney Diseases

Human embryonic stem cells offer the potential for treating a number of major diseases of concern to all of our NIDDK programs. Because of their special plasticity, these cells offer the possibility to differentiate into highly important tissue specific cells. For example, there is an intense effort underway to understand the genetic rules by which an undifferentiated cell becomes a beta cell of the islet of the pancreas, which is capable of secreting insulin. For this to happen, it is important to understand the genes that are expressed temporally that are not only related to the growth of this type of cell, but also related to its important differentiated function of recognizing glucose concentrations and responding by secreting insulin. Isolated cells of this type are used for transplantation studies and, to a limited extent, in human therapeutic approaches to treat type 1 diabetes. The embryonic stem cell could offer an unlimited supply of these cells once the rules of differentiation are known.

Other examples include attempts at cellular therapy to replace diseased liver tissue. In this case a cell would need to differentiate along the lines of a functional liver cell. Again, a similar set of rules are necessary for this to happen, but again the plasticity of the embryonic stem cell would form an excellent base for this to occur. Other examples could include various forms of kidney cells or potentially bladder cells. At the present time, there are a number of studies underway in an attempt to grow bladder cells that could be used to reconstruct a human bladder.

There are numerous other examples in addition to diabetes, liver failure, kidney failure, and urologic diseases in which human embryonic stem cells may have a major therapeutic role. It would also be important to try and understand the genetic rules of development so that these important cells may be applied to important therapeutic uses.

National Institute of Neurological Disorders and Stroke

In no area of medicine is the potential of stem cell research greater than in diseases of the nervous system. The most obvious reason is that so many diseases result from the loss of nerve cells, and mature nerve cells cannot divide to replace those that are lost. In Parkinson's disease, nerve cells that make the chemical dopamine die. In Alzheimer's disease, cells that make acetylcholine die. In amyotrophic lateral sclerosis the motor nerve cells that activate muscles die. In stroke, brain trauma, and spinal cord injury many types of cells are lost. There are many more disorders that affect both adults and young children in which nerve cells die.

It might seem hopelessly optimistic to think that supplying new cells to a structure as intricate as the brain would do any good. Can new cells become well enough integrated to restore function? The encouraging preliminary results from fetal tissue transplantation trials for Parkinson's disease argue that they can. Here, the difficulty of obtaining enough cells of the right type–that is, dopamine producing nerve cells--limits success. This year in animal experiments scientists developed methods to isolate neural stem cells and coax them to proliferate for several generations in cell culture, and then, on cue, to specialize into mature dopamine nerve cells. A large supply of "dopamine competent" stem cells will remove the barrier of limited amounts of tissue. When these cells were implanted into the brains of rodents with experimental Parkinson's disease, the animals showed remarkable improvements in their movement control. In other experiments, scientists inserted the gene for a crucial enzyme into stem cells, then transplanted these cells into animals with experimental Tay-Sachs disease, again with very encouraging results. Experimental cell replacement therapies are underway for other chronic diseases and for acute disorders like spinal cord injury and stroke. Transplant therapies for intractable epilepsy are also not out of the question. The potential for cell transplant therapies using cells derived from stem cells is enormous.

Stem cells have important uses beyond cell transplant therapy. Other possibilities include drug development and drug screening methods. One enticing possibility follows from some surprising results that were reported just last year. Contrary to a longstanding belief that nerve cells in the adult human brain cannot be replenished, scientists found neural stem cells in one part of the brains of adult, even 60 year old, humans. If we can identify the natural signals that control the proliferation and specialization of stem cells, and understand how best to encourage these restorative reactions, we may be able to help the brain repair itself in certain vulnerable regions.

The promise of stem cell research is very real, but to realize the potential of stem cells for treating nervous system diseases, we must overcome significant obstacles. We don't yet know how to control the survival and specialization of stem cells adequately. Just delivering cells to the appropriate sites within the human brain is an extremely difficult task. In addition, just as in blood transfusions, we must confront the difficulties of immune reactions. All of these factors argue for intensified efforts to understand the basic biology of stem cells in the nervous system and to apply what we know to treating disease.

National Institute of Allergy and Infectious Diseases

Transplantation: Research on embryonic stem cells could lead to cures for diseases that require treatment through transplantation, including autoimmune diseases. (Autoimmune diseases include multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and type-I diabetes).

The most feasible example over the short term is treatment of type-I diabetes by transplantation of pancreatic islet cells or beta cells produced from autologous embryonic stem cells -- that is embryonic stem cells found in the person who would be receiving the transplant. While there is substantial uncertainty with this direction, including whether embryonic stems cells can be found in children or adults, the promise is considerable. Autologous transplants would obviate the need for immunosuppressive agents in transplantation and the ensuing susceptibility to other diseases. Moreover, ultimately, embryonic stem cells might be used to create transplantable cells, tissues, and organs of any type. 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.

Primary Immunodeficiency Diseases: Embryonic stem cells might be used in treatment of virtually all primary immunodeficiencies. There are more than 70 different forms of primary (congenital and inherited) deficiencies of the immune system. Primary immunodeficiency diseases are characterized by an unusual susceptibility to infection and are sometimes associated with anemia, arthritis, malabsorption and diarrhea, and certain malignancies. They can involve considerable pain and suffering, numerous hospitalizations, high medical costs, and even death. Almost all of these diseases are rare. Because these diseases are genetic, gene replacement is an important area of investigation in the search for effective treatment. The transplantation of stem cells reconstituted with a normal gene might result in development of healthy cells of the types affected by the missing or damaged genetic material in the immunodeficiency disease. As a mechanism for gene replacement, based on research with animals, there is reason to believe that embryonic stem cells will have proliferative advantages over currently available alternatives, such as peripheral blood or bone marrow derived hematopoietic stem cells. Other hypothetical advantages include greater susceptibility to genetic transduction. Ultimately, the hope is for greater potential for engraftment, long-term survival and reconstitution of normal cellular functions.

HIV/AIDS: Research on autologous embryonic stem cell transplants (transplants to and from the self) could make restoration of immune function a viable option for treating HIV disease. Such transplants could regenerate all the components of the immune system that have been damaged by HIV infection. Research would need to demonstrate that autologous embryonic stem cells could be found in HIV-infected patients. While there are many questions to be answered, experiments in animal models point to significant advantages with the use of these cells. Primarily, the

embryonic stem cells are easily transduced with new genetic material, such as anti-HIV genes, so that the daughter cells are resistant to HIV infection. Thus, this combination of gene therapy and stem cell research could result in the immune reconstitution of AIDS patients with cells that are resistant to HIV.

National Institute of General Medical Sciences

Human pluripotent stem cells could make a significant contribution to applied trauma and burn research, such as research devoted to the development of "artificial skin." Such a biomaterial would enjoy wide application in the field of burn therapy. Initial studies, begun in the early 1980s, led to the development of a model for cultivating skin cells from burn patients. The method, which is being tested on patients today, consists of combining a biopolymer sponge made of collagen with actual skin cells from burn patients. Conceivably, human pluripotent stem cells could also be used as a source of "skin" to build such a graft, especially for severely burned patients with limiting amounts of remaining intact skin.

National Institute of Child Health and Human Development

The fundamental question in biology is how a single fertilized egg develops into a complex adult organism, with many different specialized cell types performing specific functions. This development follows a program directed by precisely timed turning on and off of many genes. Learning how this process works is basic to the mission of NICHD. Studies of stem cells of various animal models have taught us much about this process, and brought us to the point of readiness to study that process in humans at the earliest stages, using pluripotent stem cells to learn how that process is directed and controlled.

That knowledge will allow scientists, among other things, to direct the development of these cells along a certain path to become liver, blood, bone, brain, or any type of cells which then can be used in transplantation and for many other purposes described by other Institutes. Within NICHD's area of interest, these cells could be used to replace organs or tissues that are defective as a consequence of birth defects. For example, one such condition is biliary atresia, in which part of the liver does not develop correctly. Stem cells could potentially be directed to form liver tissue or intact liver to replace the damaged organ and save the life of the affected infant.

National Eye Institute

Treatment of Retinal Degenerations: Some promising results have been obtained transplanting retinal cells and tissues in an efforts to "treat" animal models of retinal degeneration. However, the results have been mixed and many questions remain. The immunologic issues governing transplant survival are complex and only partially understood. Possible strategies for overcoming these problems are suggested from ongoing investigations of the development and maturation of the normal retina. Cell lineage analysis has shown that retinal cells are generated from progenitor cells throughout development. The cell types generated in vitro can be influenced by the environment, and certain growth factors added to retinal cell cultures can lead to shifts in the types of cells produced. Growth factors can also influence the survival of retinal cells in vitro or in vivo. In addition to the effect of extrinsic cues, intrinsic properties of progenitor cells contribute to the genesis of retinal cell types as well. These types of experiments may lead to more effective strategies whereby manipulation of these progenitor cells could be exploited for retinal transplantation therapies. However, these experiments may also reveal insurmountable difficulties associated with this limited approach. In which case, use of pluripotent stem cells would become essential to overcome the immunological or other potential problems that may be encountered.

Treatment of Ocular Surface Disorders: There is a significant clinical need for improved techniques to promote conjunctival and corneal healing during disease or after injury. Conventional surgery is not consistently successful in treating persistent corneal ulcers, chemical or thermal injury, bullous keratopathy, and various cicatrical diseases. Transplantation with pluripotent stem cells could provide a means of facilitating epithelialization of the ocular surface, reducing inflammation, vascularization, and scarring.

National Institute of Environmental Health Sciences

Human stem cell research offers great promise for use in testing the beneficial and toxic effects of biologicals, chemicals and drugs in the most relevant species for clinical validity – man himself. Such studies will lead to fewer, less-costly, better-designed human clinical trials yielding more specific diagnostic procedures and more effective systemic therapies. Beyond the drug development screening of pharmacological agents for toxicity and/or efficacy, human stem cell research offers powerful new research approaches for clarifying the complex association of environmental agents with human disease processes. It also makes possible a powerful new means of conducting detailed investigations of the underlying mechanisms of the effects of environmental toxicant or mixtures of toxicants. Cancer is not the greatest health hazard of environmental toxicants at the common exposure levels with which we encounter them. Of greater concern are their subtle effects on the developing embryonic and fetal development tissue systems responsible for maintaining strong post-natal health. For example, the human embryo and fetus may be very susceptible to long-terms impairments of immune or nervous system functions from the *in utero* effects of toxicant exposure.

For example, dioxin, an environmental toxicant, is now present virtually everywhere in the environment, including in humans. How dioxin behaves in humans is poorly known with respect to its toxic effects on subtle embryonic, fetal or neonatal developmental processes whose damage may take further decades to result in overt disease expression. The use of human stem cell cultures may allow the identification of the specific early cell types at greatest risk of dioxin effects, the mechanism of the toxic effect(s) and the temporal nature of its harbored effects in the progeny of the cell lineage(s) established from such stem cells.

Parkinson's disease, according to most recent findings, has a strong environmental exposure component for one form of the disease. The nature of the agents and the timing of the exposure remain unknown at present. The use of human stem cell cultures will permit screening for the subtle effects of candidate environmental toxicants and toxicant mixtures on specific cell types in the developmental stages of the cell lineage comprising the nervous system cells and tissue associated with the brain region compromised by the disease. Such explorations may yield powerful insight into the biological mechanism(s) underlying human susceptibility to the epigenetic form of this disease with onset after age 50, as well as the genetic-based "early" onset form of the disease.

It is possible that studies using the opportunities afforded by human stem cell research will lead to molecular markers or surrogate markers or combinations of these that can be utilized for population-based studies of gene-environment interaction in disease etiology. Using the power of human stem cell toxicity screening coupled with DNA micro-array technology, it may be possible within a decade to construct complex matrices of reporter molecules that report a "signature" characteristic of very high risk for the development of a complex source human disease. Applied to newborns and children, the most vulnerable of our population, maximum opportunities for medical

health planning for intervention and prevention of disease in sensitive individuals would be possible.

National Institute on Aging

Research on human pluripotent stem cells offers potential for developing therapies to replace, repair, or modify cells damaged or lost in age-related neurodegenerative disorders, including Parkinson's disease and Alzheimer's dementias, stroke, brain trauma, and spinal cord injury. For example, in animal models and in limited human studies, researchers are exploring whether transplanting fetal dopamine-producing neurons into the brains of Parkinson's patients alleviates functional decline. The ability to characterize the experimental conditions that would achieve optimal functional recovery or to define survival properties in the host tissue has been limited by the small numbers of cells available from fetal tissue. Without stem cells, clinical efforts to repopulate cerebral nerve cells must rely upon obtaining nerve cells directly from the brain, which can be prohibitively difficult. The availability of pluripotent stem cells, that could be stimulated to become neural stem cells, might offer a promising alternative to conventional drug therapies with significant advantages for the treatment or prevention of neurodegenerative disorders. New opportunities exist to:

Assess the potential for use of pluripotent human stem cells for cell therapy in Alzheimer's and Parkinson's diseases: These stem cells can be grown in culture and then transplanted to brain areas either as pluripotent stem cells or after being treated to become a specific type of neural stem cell. For example, neural stem cells could be stimulated to eventually develop into a cell type that uses dopamine to transmit signals between nerve cells. These cells could then be grown in culture to provide a potentially unlimited supply of cells that could be transplanted into the brains of Parkinson's disease patients to replace lost dopamine-producing neurons. Similar approaches could be developed to replace the dead or dysfunctional cells in cortical and hippocampal brain regions affected in patients with Alzheimer's disease. Stem cells could also be used to replace glial cells, which help maintain the myelin sheath around nerve fibers, in multiple sclerosis and other diseases characterized by loss of this protective sheath.

Use stem cells as vectors for delivering genes or other therapeutic substances, such as neurotrophic or growth factors, to defined brain regions: Stem cells could be genetically modified to express one or more neurotransmitters or growth factors to provide a continual source of these molecules after transplantation. Again, research in animals is showing great promise in adapting stem cells to carry molecules into the brain that would protect it from injury or hasten repair. In other experiments, transplantation of cells engineered to produce specific growth factors is being tested as a therapy for loss of dopamine cells in animal models of aging and of Parkinson's disease.

Current research in animals is determining the factors that induce stem cells to differentiate into specific neuronal cell types. Importantly, this research has shown that stem cells transplanted into the adult brain can survive and can be induced to form differentiated neurons appropriate for the brain targets in which they are placed, with the promise of functional integration into brain circuits. Stem cell research may also

help improve understanding of glial and neural cell regulation. Continued studies are needed to determine how and to what extent neural stem cells
are functionally integrated into brain circuits and whether they can replace dead cells or promote recovery of dysfunctional cells resulting from injury, neurodegeneration, or aging.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Generation of replacement cells and tissue to treat diseases: Because stem cells constitute a 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. Equally important, if a self-renewing population of new 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 the stem cells from a healthy donor to a recipient, or by genetically modifying a person's own stem cells and returning them to the marrow. Such an approach holds great promise for genetic disorders of bone and cartilage, such as osteogenesis imperfecta and the various chondrodysplasias. In a somewhat different application, stem cells could be stimulated in culture to develop into either bone or cartilage-producing cells. These cells could then be introduced into the damaged areas of joint cartilage in cases of osteoarthritis, or into large gaps in bone that can arise from fractures or surgery. This sort of repair would have a number of advantages over the current practice of tissue grafting.

Improve understanding of normal and abnormal development: The ability to isolate and manipulate stem cells in culture will provide experimental access to the processes that regulate the differentiation of bone and cartilage cells. This will enable investigators to identify the molecules that control the proliferation of stem cells, or induce or inhibit stem cells' progression to mature functional cell types. In turn, testing for the presence and activity of these regulatory molecules in healthy and diseased tissues will indicate conditions in which defects of stem cell regulation or differentiation underlie pathology.

Improve development and testing of drugs: A detailed understanding of stem cell regulation and the molecules that affect it would provide new targets for pharmacological interventions. Stem cell culture systems would also make possible rapid and economical testing of candidate agents for both effectiveness and safety.

National Institute on Deafness and Other Communication Disorders

Stem cell research offers the possibility of potentially replacing the sound-detecting hair cells in the inner ear that are often lost due to genetic, infectious, traumatic, or pharmacologic causes. Many scientific advances must occur before it would be rational to attempt to use stem cells to replace lost hair cells, including research advances that would prevent immune rejection of stem cells. In addition, research advances will be needed to define the molecular events that lead stem cells to a differentiation pathway that generates highly specialized hair cells, and not other specialized cells. Having noted these caveats, an opportunity would be lost if investigators were unable to obtain NIH support to determine the full potential of stem cells for replacing differentiated cells that are lost or damaged.

National Institute of Mental Health

There is good evidence that many of the mental and behavioral disorders such as schizophrenia, autism, manic-depressive illness and memory disorders, result from permanent disruption of brain circuitry or brain chemistry.

The National Institute of Mental Health (NIMH) is currently supporting many research grants to determine exactly where and how such brain disruptions may occur, and is encouraging a vigorous program of research, including stem cell research with animals to develop disease models and understand basic neuronal processes. For example, scientists are using non-human primate models to explore the hypothesis that schizophrenia is the result of damage to brain cells that mature at a particular stage of in human development. If this hypothesis proves true, pluripotent stem cells might provide a window into what goes wrong in the developmental processes of these such brain cells.

In another arena, investigators are examining stress- and toxin-induced loss of cells in a brain structure important for memory, the hippocampus. Animal studies have shown that natural replacement of cells in the hippocampus, via stem cells, results in improved memory performance as long as another important structure for memory, the cerebral cortex, is largely intact. Human pluripotent stem cells might ultimately be important to the development of replacement cells in the hippocampus of humans suffering from memory loss caused by selective damage to the hippocampus.

National Institute on Drug Abuse

Refinement of stem cell technology will provide an additional tool for scientists to study drugs of abuse. For example, although we are currently not supporting any stem cell research, NIDA-supported researchers can potentially use stem cells to reverse some of the long-term effects of drugs. Pluripotent stem cells offer a potential means of replacing neurons destroyed by drug abuse. This will be especially useful for individuals who have abused drugs such as methamphetamine, MDMA (ecstacy) and inhalants which have been shown in animal and some human studies to cause long-term, possibly permanent damage to selected areas of the brain. For example, recent research has shown that methamphetamine can have significant toxic effects on dopaminergic and serotonergic neurons in the brain. This is of particular concern because of the spreading use of this drug and may be related to the dramatic behavioral effects, including the development of psychotic-like behavior patterns that methamphetamine can have in some people. Pluripotent stem cells stimulated to develop into dopaminergic, serotonergic or other types of neurons, could offer a potential means of replacing neurons destroyed by drug abuse. In this way, we may be able to eventually reverse some of the debilitating behavioral effects of drugs such as methamphetamine. Damage to peripheral organs (i.e., cocaine-induced cardiac damage) may also eventually be treated by "replacement" organs generated from such stem cells.

Stem cells can also be valuable tissue sources for screens to study the effects of drug exposure on specific cell types. This could help researchers determine whether in utero exposure to drugs such as methamphetamine is neurotoxic and which cell types are particularly vulnerable. In this way, researchers will better understand the effects that prenatal exposure to drugs of abuse have upon the developing fetus, thereby gaining knowledge critically important to the improvement of the public health of neonates, infants, and children which cannot be learned through studies on humans themselves.

National Institute on Alcohol Abuse and Alcoholism

Pluripotent stem cell research offers significant potential for advances in the treatment of alcohol-associated organ pathology and in preventing or treating fetal alcohol syndrome. The value of pluripotent stem cell research would be in elucidating mechanisms of cellular differentiation. With this knowledge, scientists would have the potential to selectively differentiate cells into various tissues. The following examples demonstrate the potential utility of this type of research to the alcohol field:

Alcohol-induced pathology: Alcohol is a major source of damage to organs, such as the liver and brain, that may or may not regain function with abstinence from drinking. Development of medications that accelerate recovery in organs damaged by alcohol would be a major breakthrough. Such an advance would lessen human suffering and the economic burden associated with alcohol-induced organ damage. Stem cell research would provide a cost-effective means of discovering mechanisms that underlie alcohol-related pathology and that could be targets for new medications. For cases of irreversible organ damage, stem cell research could be used to facilitate generation of new organ tissue.

Fetal alcohol syndrome (FAS): Pluripotent stem cells would provide FAS investigators with a tool to study how alcohol disrupts cellular differentiation at various stages of embryonic development. Findings from this research would contribute to the design of potential interventions for FAS.

National Center for Research Resources

Many scientists believe that it one day may be possible to grow replacement organs in tissue culture from cells that have been specifically programmed. Already, skin is routinely grown in large sheets and used to replace skin destroyed by burns or other types of injury. But before complex tissues from the brain, heart, pancreas or liver can be reliably reproduced, years of research lie ahead. Studies on pluripotent cells, known as stem cells, can provide important information on how the different organ systems in the body develop and how this development can be controlled and put to good use. Unfortunately, stem cells still are difficult to isolate and culture. NCRR will support the development of a nonhuman stem cell resource to facilitate this important research. Such stem cell studies may eventually lead to effective treatments for Alzheimer's and Parkinson's disease and possibly other degenerative brain disorders as well as to the production of insulin-producing pancreatic beta cells to treat diabetics who no longer can make their own insulin. It may also be to generate replacement heart valves and functional liver tissue.

National Institute of Nursing Research

Nursing research will benefit from the technological advances from human pluripotent stem cell research. For example, investigators in our Intramural Wound Healing Laboratory could grow skin tissue to be used for grafts in chronic wounds, using the patients' own tissue. Nursing research will also address issues such as patient and family decisionmaking about the use of stem cells as treatment. When stem cell clinical applications involve patient care, nursing research studies will contribute to the science base for health care professionals, especially nurses.

National Human Genome Research Institute

The National Human Genome Research Institute is using the tools produced by the Human Genome Project to study the fundamental mechanisms of development and the contributions of genetic factors to disease. NHGRI investigators have identified the following as potentially promising areas of study involving pluripotent stem cells:

Gene Expression: The differentiation potential of pluripotent stem cells make them important candidates for studies of alterations in gene expression profiles. Being able to examine the genes that are turned on and off during the differentiation process of these cells using newly developed microarray technology could supply very useful information about normal and abnormal cell development. This information could have promising application to a whole host of disease areas.

Parkinson's Disease (PD): PD is caused by degeneration of neurons in a region of the brain, the substantia nigra, leading to severe abnormalities in movement. The cause is largely unknown, although in a few rare families with early onset disease, mutations in the gene for alpha synuclein are known to be responsible. As with other neurodegenerative disorders, replacement of damaged nerve cells with stem cells is one avenue of possible therapy. Current experiments using fetal cells for replacement have provided very mixed results, especially in the long-term. One possible explanation for the less than complete replacement is that the cells being transplanted are too far along in path of development and differentiation to be able to take up residence in the substantia nigra, make all the correct connections, and replace the damaged cells. Using even less differentiated cells, such as embryonic stem cells, is a possible alternative.

Gene Therapy: Almost any genetic disease where cell and tissue transplantation protocols exist could potentially benefit from the application of embryonic stem cells in gene therapy. For example, patients with genetic disorders of immunity might benefit greatly from studies involving gene transfer using specially derived pluripotent stem cells. Studies involving these cells may also be useful in immune reconstitution or engineering viral resistance for HIV infected individuals.

Blood Disorders/Sickle Cell Disease: The epsilon globin gene is expressed only in embryonic red blood cells. This gene recently has been shown to block the sickling of the sickle cell hemoglobin. Research involving embryonic stem cells could help answer questions about how to turn on the epsilon globin gene in adult blood cells and thereby halt the disease process. Stem cell research may also help produce transplantable cells that would not contain the sickle cell mutation.

(Billing Code 4140-01-P)
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
Notice of Meeting of the Working Group to Advise the ACD on Guidelines and Oversight Process for Research Involving Human Pluripotent Stem Cells

Notice is hereby given that the Working Group of the Advisory Committee to the Director (ACD), NIH to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells, will meet in public session at the Bethesda Marriott, 5151 Pooks Hill Road, Bethesda, Maryland 20814, on April 8, 1999. The meeting will begin at approximately 9:00 a.m. and end at approximately 5:30 p.m.

The goal of the Working Group is to provide advice to the ACD about the scientific, ethical, legal, and social issues relevant to guidelines for the conduct of research utilizing human pluripotent stem cells (cells that can form most of the cells and tissues of the body) and to consider oversight options for this research.

A limited amount of meeting time will be allotted for public testimony. Individuals who wish to give five minute public testimony may sign up at the meeting site the morning of the meeting on a first come, first served basis. Written testimony may be submitted to: the Office of Science Policy, Bldg. 1, Room 218, NIH, 9000 Rockville Pike, Bethesda, 20892.

Attendance may be limited to seat availability.

Dated:

_____

Ruth L. Kirschstein, M.D.

Deputy Director, NIH

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tony Mazzaschi <Tmazzaschi@aamc.org> (Tony Mazzaschi <Tmazzaschi@aamc.org> [UNKNOWN])

CREATION DATE/TIME:31-MAR-1999 13:57:25.00

SUBJECT: Adhoc: Meeting of Stem Cell Working Group Announced

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
The NIH has announced a public meeting of the ACD working group on research involving human pluripotent stem cells on April 8 in Bethesda. During the meeting, the working group is making time available for public testimony. The NIH notice follows.

Tony Mazzaschi
AAMC

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the ACD on guidelines and oversight for research involving human pluripotent
stem cells, will meet in public session at the Bethesda Marriott, 5151 Pooks
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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tony Mazzaschi <Tmazzaschi@aamc.org> (Tony Mazzaschi <Tmazzaschi@aamc.org> [UNKNOWN])

CREATION DATE/TIME: 6-APR-1999 09:01:58.00

SUBJECT: Adhoc: Chairman Specter: "Determined to Raise NIH By $2 Billion"

TO: clinicalmail@aamcinfo.aamc.org (clinicalmail@aamcinfo.aamc.org [UNKNOWN])
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TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
An article in this morning's Washington Post on the budget spending caps concludes with the following paragraph:

"Sen. Arlen Specter (R-Pa.), chairman of the Senate subcommittee on labor, health and human services and education, worries about the National Institutes of Health, for him "the No. 1 item" in a budget that exceeds $60 billion. "You get more results from NIH funding than anything else," Specter said. Stem cell research, he said, could cure Parkinson's disease "within 10 years," and he is "determined to raise NIH by $2 billion," caps or no caps."

The full article follows.

Tony Mazzaschi
AAMC

The Straitjacket of Strict Spending Limits Congressional Chairmen Find Constraints Easy to Endorse, Hard to Live With

By Guy Gugliotta and George Hager
Washington Post Staff Writers
Tuesday, April 6, 1999; Page A04

Congressional Republicans have muscled through a budget proposal that sticks to strict spending limits and allows the GOP to cast itself as the guardian of fiscal discipline. But the Republican subcommittee chairmen charged with implementing the plan later this year have a message for their colleagues: It won't work.

Senior appropriators say their leaders have put them in a straitjacket. They must provide large increases to fund GOP priorities in defense and education, absorb huge military emergencies such as Kosovo and still hold overall spending at least $9 billion below last year.

This is a zero-sum game, and appropriators warn that they will have to make drastic, politically dangerous and, some say, unrealistic cuts in beloved projects and programs to make the numbers balance out. Lawmakers may lose the bridges and highway overpasses that ease the path to reelection, the appropriators say. Maintenance at national parks may suffer. Energy research may have to be abandoned, and funding for the National Institutes of Health reduced. The Coast Guard may have to terminate shipbuilding contracts.

Interviews with most of the 26 chairmen of the House and Senate Appropriations subcommittees that fund the federal government revealed widespread doubt that the spending limits can be maintained and exasperation with colleagues who refuse to exceed them even as they demand funding for pet programs and projects.

"There's an awful lot of people around here who don't want to give something to get something," said Sen. Ben Nighthorse Campbell (R-Colo.), chairman of the Appropriations subcommittee that funds the Treasury Department, the Postal Service and numerous White House agencies. "You never say never, if you can't follow through."
"I don't think we can live under these [spending] caps," said Senate Appropriations Committee Chairman Ted Stevens (R-Alaska).

The spending caps apply to $536.3 billion of the $1.7 trillion federal budget, the so-called discretionary funds that pay for the vast government bureaucracy and most of what it does every day, including programs as diverse as energy research, highway building and maintaining U.S. forces in the Balkans. The current caps were imposed in 1997 as part of a strategy for gradually reducing federal spending to bring the budget within balance in five years.

Although the booming economy helped balance the budget four years ahead of schedule, the caps have stayed in place and, indeed, are already proving to be much too tight for lawmakers to live with. Bipartisan pressure for more money last year provoked a showdown in which President Clinton demanded and got more money for his priorities, while Republicans seized the opportunity to add money for theirs.

The result was about $21 billion in "emergency" spending above the 1999 caps -- an embarrassing experience that the GOP has vowed never to repeat.

The Republican leadership is anxious to maintain the high ground in its battle with Clinton over who is the more zealous protector of Social Security; at this point, any spending above the caps would dip into money both parties say should be used for shoring up the massive

retirement program.

But many appropriators warn that fiscal purity will ultimately be overwhelmed by the practical reality that both parties want more money and will eventually be willing to bust the caps to get it. Indeed, the House has already exceeded the caps, passing a bill last month that included $195 million to reimburse the military for hurricane relief in Central America. Appropriators said that was just a harbinger of much more to come. They noted that by sticking with the caps in strict Republican budget proposals approved in March, the GOP is headed down a blind alley.

"This plays into the White House's scheme," said Rep. Harold Rogers (R-Ky.), chairman of the House Appropriations subcommittee that funds the departments of Commerce, Justice and State. Rogers noted that a year-end negotiation like last year's "is the only time" Clinton gets such extraordinary power to dictate to the GOP Congress on spending bills.

A few top appropriators, however, insist that staying below the caps is doable and desirable. "We need this type of discipline," said Rep. Sonny Callahan (R-Ala.), whose subcommittee provides foreign aid. "If Congress tells me to make reductions in foreign assistance, it's easier for me. I'm not a big proponent of foreign assistance."

Doable or not, the experience promises to be excruciating. Fiscal 2000's $536.3 billion discretionary spending cap is at least $9.6 billion below last year's, according to Congressional Budget Office figures, and may be as much as $25.4 billion less, if emergency spending from last year continues.

Add a proposed $10 billion increase for defense, $3 billion for education, billions more in Senate-approved military pay raises and deployments in the Balkans and elsewhere, and the pain of staying under the cap could quickly become unbearable.

With no other choice for now, appropriators are preparing to draw up bills that comply with the caps, and they are looking at trade-offs their colleagues won't like. It's "like a teeter-totter," said Rep. Ralph Regula (R-Ohio), chairman of the House subcommittee on Interior and related agencies. "If education and defense go up, it means less on the other end of the board."

Sen. Richard C. Shelby (R-Ala.), whose subcommittee funds the Transportation Department, said the combination of the caps and the GOP budget would leave him about $2.2 billion below the White House request in actual spending. Subcommittee Democrats said compliance would require zeroing out Amtrak, ending plans to modernize air traffic computer systems, canceling all Coast Guard shipbuilding contracts, terminating all 8,500 members of the Coast Guard Reserve and cutting the Coast Guard and FAA operating budgets by 11 percent.

"It'll be terrible," said Rep. Frank R. Wolf (R-Va.), Shelby's House Appropriations counterpart. "You would end Amtrak, and you would

pretty much devastate the Coast Guard."

Regula turns to legislative triage to cope with difficult times. First come "must do" priorities -- "We've got to keep the national parks open," he said. Next is "need to do" -- clearing the backlog of maintenance at the parks.

"And then there's 'nice to do' -- build a visitors' center, or acquire a piece of land," Regula said. With the caps, "nice to dos" are gone, he said, and maintenance may have to wait.

Sen. Slade Gorton (R-Wash.), Regula's Senate counterpart, likes to fund special projects and notes that "I am clearly the most popular man in the Senate when my subcommittee is meeting."

He worries about the future of Philadelphia's Independence Mall, "a great, great idea" and a personal favorite. Regula likes fossil fuels research and bemoans the possible future of a $100 million Energy Department joint project with automakers to develop an 80 miles-per-gallon car.

For House energy and water subcommittee Chairman Ron Packard (R-Calif.), the caps mean the government probably will not be funding any new dams or environmental restoration projects, both of them perennial favorites of members.

Also at risk, Packard said, are little-known but very important programs like the purchase and disposal of weapons-grade plutonium and uranium from foreign countries so the material won't fall into the wrong hands. "We may not be able to fund all of that," Packard said.

Sen. Arlen Specter (R-Pa.), chairman of the Senate subcommittee on labor, health and human services and education, worries about the National Institutes of Health, for him "the No. 1 item" in a budget that exceeds $60 billion. "You get more results from NIH funding than anything else," Specter said. Stem cell research, he said, could cure Parkinson's disease "within 10 years," and he is "determined to raise NIH by $2 billion," caps or no caps.

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME: 7-APR-1999 12:40:33.00

SUBJECT: FW: draft agenda and charge

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

TEXT:
Commissioners et al.,

I will be attending two meetings this week on stem cell research, the outcomes
of which may be of direct interest to our work. The first (this afternoon) is
being held by the AAAS. They (and the Institute for Civil Society) a convening a
2-day working group meeting to look at all aspects of this issue. Like other
working group meetings of the AAAS, the format involves several presentations
given by experts and others before a working group. The working group includes:
Andrea Bonnicksen, David Byers, Courtney Campbell, Cythia Cohen, Dena David,
Abigail Evans, Kevin Fitzgerald, Norm Fost, Robert Goldman, Robert Goldstein,
Ron Green, David Gottlieb, Ben Mitchel, Daniel Perry, Robert Wachbroit, Gillian
Wollett.

Presenters, (besides me), include Lana Skirboll (NIH), Daniel Marshak (Osiris
Therapeutics), Robert Goldstein (Juvenile Diabetes Foundation), Karen
Lebacqz/Laurie Zoloth (both of the Geron Ethics Advisory Board).

It is expected that the working group will develop a 'Statement"..... if
this is available by next week, I'll share it with you at the meeting in
Charlottesville.

The second meeting is of NIH's working group. I've enclosed the agenda, and the
participant's list and charge below in text, and the agenda in an attachment
I've been asked to discuss the staff draft points to consider--which I'll do

with appropriate caveats, etc. I'll give you an update following the meeting.

Eric

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

-----Original Message-----
From: Borror, Kristina (OD)
Sent: Wednesday, April 07, 1999 8:46 AM
To: Meslin, Eric (OD)
Cc: Kawazoe, Robin (OD); Skirboll, Lana (OD)
Subject: draft agenda and charge

<<agenda4.wpd>> <<charge_2.wpd>>
Charge to the Working Group

The Department of Health and Human Services (DHHS) has concluded that current
law permits Federal funds to be used for research utilizing human pluripotent
stem cells. The National Institutes of Health (NIH) understands and respects
that there are compelling ethical, legal, and social issues relevant to
pluripotent stem cell research and plans to move forward in a careful and
deliberate fashion. Rigorous guidelines that address the aforementioned issues
will be developed and stringent oversight that goes beyond the traditional NIH
scientific peer review process will be put in place.

The charge to the Working Group is to provide advice to the Advisory Committee
to the Director (ACD) about the scientific, ethical, legal, and social issues
relevant to guidelines for the conduct of research utilizing human pluripotent
stem cells. The scope of the advice should include identification of the areas
of this research that should be eligible and ineligible for Federal funding;
documentation that investigators who wish to use human pluripotent stem cells

should provide regarding the source of the cells, informed consent, plans for
use, and other pertinent information; and options for review and oversight of
this research. The Working Group will consider advice from the National Bioethics Advisory Commission (NBAC), the public, and the Congress.

The advice provided, if accepted by the ACD, will be used to develop draft guidelines for human pluripotent stem cell research, which will be published in
the Federal Register for public comment. The final guidelines, taking the public comments into consideration, will then be published in the Federal Register and will be used in the oversight process.

Participants
Working Group to Advise the ACD on Guidelines and
Oversight Process for Pluripotent Stem Cell Research

Co-Chairs:

Shirley M. Tilghman, B.Sc., Ph.D.
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Department of Molecular Biology
Princeton University
Princeton, NJ

Ezra C. Davidson, Jr., M.D.
Associate Dean, Primary Care
Professor and Past Chairman
Department of Obstetrics and Gynecology
Charles R. Drew University of Medicine
and Science
Los Angeles, CA

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Chestnut Hill, MA

Constance L. Cepko, Ph.D.
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President
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Brigid Hogan, Ph.D.
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Eastern Virginia Medical School
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Charlie Queenan
Patient Advocate
Washington, D.C.

Carol Tauer, Ph.D.
Professor
Department of Philosophy
College of St. Catherine

St. Paul, MN

Draft Agenda for Working Group to Advise the ACD on Guidelines and Oversight for
Human Pluripotent Stem Cell Research

9:00am Welcome and Charge (Varmus)

9:15am Presentation of Legal Opinion)

9:30am Format for the day's discussion (Marcy Wilder)

9:45am The Science of Pluripotent Stem Cells

10:15am Public Comment Period

11:00am Presentation of Draft NBAC "Points to Consider" (Meslin)

11:30am Discussion of Possible Elements in Research Guidelines

* abStudies with pluripotent stem cells that are ineligible for
Federal funding

12:00pm Lunch

1:00pm Continuation of Discussion of Guidelines

* abStudies with pluripotent stem cells that are eligible for
Federal funding

- Issues regarding sources of cells

* ab cells derived from human embryos in excess of clinical
need
- Informed Consent Issues

* ab cells derived from fetal tissue
- Informed Consent Issues

3:00pm Presentation of Possible Options for Oversight

Process

3:30pm Discussion of Oversight Options

5:00pm Summary

5:30pm Adjourn

Marcy Wilder

Shirley Tilghman and Ezra Davidson

Brigid Hogan

Eric Meslin

Working Group Members

Wendy Baldwin

Working Group Members

Shirley Tilghman and Ezra Davidson

- agenda4.wpd - charge_2.wpd========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:
Unable to convert ARMS_EXT:[ATTACH.D39]MAIL41428301X.136 to ASCII,
The following is a HEX DUMP:
========== END ATTACHMENT 2 ==========

April 6, 1999

Draft Agenda for Working Group to Advise the ACD on Guidelines and Oversight for Human Pluripotent Stem Cell Research

9:00am	Welcome and Charge	Harold Varmus
9:15am	Presentation of Legal Opinion	Marcy Wilder
9:30am	Format for the day's discussion	Shirley Tilghman and Ezra Davidson
9:45am	The Science of Pluripotent Stem Cells	Brigid Hogan
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	· Studies with pluripotent stem cells that are ineligible for Federal funding	
12:00pm	Lunch	
1:00pm	Continuation of Discussion of Guidelines	
	· Studies with pluripotent stem cells that are eligible for Federal funding	
	– Issues regarding sources of cells	
	· cells derived from human embryos in excess of clinical need – Informed Consent Issues	
	· cells derived from fetal tissue – Informed Consent Issues	
3:00pm	Presentation of Possible Options for Oversight Process	Wendy Baldwin
3:30pm	Discussion of Oversight Options	Working Group Members
5:00pm	Summary	Shirley Tilghman and Ezra Davidson
5:30pm	Adjourn	

Charge to the Working Group

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The charge to the Working Group is to provide advice to the Advisory Committee to the Director (ACD) about the scientific, ethical, legal, and social issues relevant to guidelines for the conduct of research utilizing human pluripotent stem cells. The scope of the advice should include identification of the areas of this research that should be eligible and ineligible for Federal funding; documentation that investigators who wish to use human pluripotent stem cells should provide regarding the source of the cells, informed consent, plans for use, and other pertinent information; and options for review and oversight of this research. The Working Group will consider advice from the National Bioethics Advisory Commission (NBAC), the public, and the Congress.

The advice provided, if accepted by the ACD, will be used to develop draft guidelines for human pluripotent stem cell research, which will be published in the Federal Register for public comment. The final guidelines, taking the public comments into consideration, will then be published in the Federal Register and will be used in the oversight process.

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME: 9-APR-1999 12:16:39.00

SUBJECT: FW: Washington Fax April 9, 1999

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

TEXT:
See today's news about the NIH meeting on stem cells, held yesterday.

Eric M. Meslin, Ph.D
Executive Director
National Bioethics Advisory Commission
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Rockville, Maryland 20892-7508
Tel: (301) 402-4242
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-----Original Message-----
From: Washington Fax [SMTP:subscriptions@washington-fax.com]
Sent: Friday, April 09, 1999 2:50 AM
To: fax@washington-fax.com
Subject: Washington Fax April 9, 1999

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April 9, 1999

Today's Washington Fax online is available at:
http://www.washingtonfax.com/p1/index.html

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NIH ADVISORY PANEL BEGINS FORGING GUIDELINES FOR STEM CELL RESEARCH
ACCEPTABLE SOURCES, INFORMED CONSENT, SAFEGUARDS AMONG MEETING TOPICS

http://www.washingtonfax.com/p1/1999/19990409.html

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NIH ADVISORY PANEL BEGINS FORGING GUIDELINES FOR STEM CELL RESEARCH

ACCEPTABLE SOURCES, INFORMED CONSENT, SAFEGUARDS AMONG MEETING TOPICS

Moving the National Institutes of Health closer to actually funding experiments with human embryonic stem cells, an agency-appointed panel began deliberations Thursday to craft guidelines designed to both provide scientists with clear parameters for such work and show Congress and the public that the agency is proceeding with great care.

The working group of the NIH director's advisory committee was established to come up with guidelines that address such matters as whether stem cells were obtained from material donated with proper informed consent and to set boundaries on the kinds of experiments that would be eligible for federal support.

The panel is co-chaired by Shirley Tilghman, a life sciences professor at Princeton University, and Ezra Davidson, associate dean at Charles R. Drew University of Medicine and Science. Its membership is comprised mainly of persons with a medical or research background, but also includes a lawyer, a professor of philosophy and two patient advocates.

The effort to craft guidelines is in an outgrowth of the agency's announcement earlier this year that a federal law forbidding funding for experiments with human embryos does not apply to work with stem cells derived from them. That means NIH grantees may soon be able to conduct research with stem cells obtained from human embryos, even though they are forbidden from working directly with the embryos themselves.

This puts the agency in the position of needing guidelines that are directed both at its grantees and at the entities that would serve as cell suppliers, be they researchers working with non-federal funds or private companies. But many observers believe comprehensive guidelines, however cumbersome, could help the agency show members of Congress that stem cell research can move forward in an ethically acceptable manner, thus staving off an anticipated move to rewrite the embryo research ban to explicitly block support for stem cell experiments.

Stem cells, which also can be obtained from aborted fetuses, are, in their so-called "pluripotent" state, believed to be capable of forming almost any cell in the human body. Recently, scientists have observed such cells in laboratory cultures "differentiating" into muscle, nerve and blood cells, prompting speculation that stem cells could be an abundant source of transplantable tissue for a range of conditions, from Parkinson's to heart disease.

The potential therapeutic application of stem cell research has sparked a clamor for public funding and has prompted NIH to seek a way to support stem cell experiments within the confines of the embryo ban. And with its decision to allow funding drawing heavy fire from the instigators of the ban, agency supporters say it's particularly important for NIH to demonstrate that it's sensitive to public misgivings.

NIH Director Harold Varmus, in remarks to the working group, said he wants the panel to draft guidelines for federally supported experiments that set criteria for an acceptable source of stem cells and the manner in which

they are derived, while also establishing boundaries on federally-supported research.

For example, a draft set of guidelines under consideration by the panel would prevent grantees from injecting stem cells into a human embryo to form a "chimeric" embryo (which would be a blend of two people's genetic material) or from using stem cells to clone a human being.

In addition, Varmus also asked the panel to provide advice "on the kinds of mechanisms that ought to be employed to ensure that all research supported by the NIH is in compliance with the guidelines." For example, once the guidelines are established, NIH plans to convene a stem cell committee to assure that applicants for stem cell research funding are in compliance with the guidelines.

"I feel strongly about this matter of oversight," Varmus said, "because this is the way we will be able to report to the public and to Congress on the detailed activities being carried out by the NIH-supported investigators in this arena."

Varmus said he expected the panel would make significant headway in its deliberations Thursday, as he hopes to soon see a proposed set of guidelines published in the Federal Register. He said the guidelines would be subject to a 60-day public comment period, after which they would be revised, if necessary, and then put before his advisory committee for approval.

Among the guidelines under consideration include:

*Stem cells used by federal researchers would be restricted to two sources: those derived from so-called "spare embryos," i.e. Those originally created for a pregnancy but are either unsuitable for implantation or in excess of what's needed, and those derived from fetal tissue. (Unlike embryos, experiments with fetal tissue, subject to certain conditions, are eligible for federal funding. However, stem cell experts say there are certain differences between stem cells derived from fetuses and those culled from embryos that make it scientifically prudent to fund work with cells from both sources.)

*Investigators using stem cells derived from human embryos would be required to provide documentation that the embryos were originally created for an infertility treatment, not for research.

*Investigators also would have to provide documentation that the source embryos were obtained through a rigorous informed consent process that clearly separated donors from the research and in no way sought to influence the donors' choice of giving spare embryos to science.

*Informed consent would involve discussing with donors the possibility that their embryos could be used to obtain stem cells and that those stem cells might lead to the development of commercial products.

The group planned to revise its guidelines based on Thursday's discussions, which touched on such issues as the challenge of crafting informed consent

standards that address the many parties involved: embryo donor, fertility clinic physician, the entity deriving the stem cell from the embryo, and the federally funded researcher who would perform the actual experiments with the stem cells.

Also featured at Thursday's meeting were public comments from both supporters and opponents of stem cell research, including a staff member of the House Pro-Life Caucus, who reiterated that caucus members believe the embryo research funding ban applies to stem cell experiments.

However, Tilghman, the working group co-chair, noted that the working group was not charged with deciding whether stem cell research should be funded.

"Our charge clearly is that if research is going to be conducted, what are appropriate guidelines" for research to be conducted in an ethically sound manner," she said.

--Matthew Davis

Compiled and Published by: WASHINGTON FAX: AN INFORMATION SERVICE
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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Evelyn Groom <egroom@Princeton.EDU> (Evelyn Groom <egroom@Princeton.EDU> [UNKNOWN])

CREATION DATE/TIME:13-APR-1999 14:19:13.00

SUBJECT: Charlottesville update

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

TEXT:
Memorandum

Date: April 13, 1999

To: NBAC

From: Harold T. Shapiro, Ph.D.

Subject: Upcoming Meeting

I want to take this opportunity to share my thoughts and plans with you regarding our meeting this week in Charlottesville.

Unfortunately, I am unable to attend the first day of the meeting. I have asked Alta Charo to chair the meeting the first day; much of the focus is on the Human Biological Materials report. I would hope that by the end of our discussion of that report, mid morning on Friday, we will have come to general agreement about the recommendations and the contents of the report. If we can achieve that goal, then we should be able to vote on the final language of the recommendations at our May meeting. Please come to the meeting prepared to give staff your detailed comments on the text. A revised ethics chapter will be made available to you at the meeting.

As for the stem cell report, staff has provided us with a blueprint for the ethics analysis and the full report. We have spent considerable time at previous meetings discussing the use of fetal tissue in such research, and to some extent, the use of embryos remaining after infertility treatments. At this meeting I hope we can settle on the general approach for any conclusions and recommendations we might develop in these two areas. We should also devote a significant amount of our discussion to the issues surrounding the production of embryos for research purposes, either through cloning techniques or traditional IVF. It will be crucial that we leave the meeting giving staff a clear guide for the development of the first draft of the report.

I have also decided that it would be helpful to hear the viewpoints from scholars and religious thinkers regarding their perspectives on the issues before us. I have asked staff to identify a date in the next few

weeks for such a meeting. I realize this is short notice, but I hope that a significant subgroup of the commission will be available for this meeting. More information will be available in Charlottesville.

I look forward to seeing you on Friday and regret that I cannot join you the first day.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Rodrigues, Dennis (OD)" <RodriguD@OD31TM1.OD.NIH.GOV> ("Rodrigues, Dennis (OD)" <RodriguD@OD31TM1.OD.NIH.GOV> [UNKNOWN])

CREATION DATE/TIME:15-APR-1999 15:03:42.00

SUBJECT: INTERIM RESULTS OF LARGE TRIALS OF HIGH-DOSE CHEMOTHERAPY WITH BO NE MARROW OR STEM CELL TRANSPLANTS FOR BREAST CANCER

TO: HHSPRESS@LIST.NIH.GOV (HHSPRESS@LIST.NIH.GOV [UNKNOWN])
READ:UNKNOWN

TEXT:
NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

NEWS RELEASE

EMBARGOED FOR RELEASE
Thursday, April 15, 1999
9:00 a.m. EST

NCI Press Office
(301) 496-6641

INTERIM RESULTS OF LARGE TRIALS OF HIGH-DOSE CHEMOTHERAPY WITH BONE MARROW OR STEM CELL TRANSPLANTS FOR BREAST CANCER

For the first time since the introduction of high-dose chemotherapy for breast cancer with bone marrow or stem cell transplants (HDC/BMT), patients and their physicians have data from large scientific studies comparing this treatment to standard therapies.

The new data come from five separate clinical trials, preliminary summaries of which were released April 15 by the American Society of Clinical Oncology (ASCO). In four of the five studies, investigators found no statistically significant difference in survival between patients receiving HDC/BMT and those receiving lower-dose chemotherapy without transplants. In the remaining trial, from South Africa, there was a significant difference in favor of HDC/BMT.

The five studies were all randomized, controlled (phase III) clinical trials, which directly compare one cancer treatment to another. Four of the trials (two in the United States, one in Scandinavia, and one in South Africa) each involved hundreds of patients and will be presented in a plenary session at ASCO's annual meeting, May 15-18, in Atlanta. The fifth trial, in France, involved fewer

patients and will be presented as a poster session during the same meeting.

"The hypothesis going into these trials, our hope, was that the more aggressive approach would prove clearly superior to standard therapy," said Richard Klausner, M.D., director of the National Cancer Institute (NCI), which sponsored the two U.S. trials. "But based upon these studies, high-dose therapy has not yet been shown to be superior to lower-dose treatment. These studies do suggest it is at least equivalent in terms of overall survival, but the added toxicity and costs of high-dose treatment require that it be superior if it is to become a standard of care."

Klausner pointed out that the positive results of the smaller South African study should not be disregarded. "The chemotherapy agents used in this trial were different from those in the other trials and the particular approach employed by the South Africans may be responsible for the positive results," he said.

The five trials have added greatly to our knowledge, said Robert Wittes, M.D., director of NCI's Division of Cancer Treatment and Diagnosis. "Up to now, breast cancer patients have had to rely on results from small feasibility studies when making decisions about this aggressive therapy," he said. "Now they have the more reliable information that can be obtained only from phase III trials. The information from these studies, viewed collectively, does not suggest that high-dose chemotherapy with transplants improves survival."

Wittes did add, however, that "the duration of follow-up is still relatively short, additional data will continue to be gathered, and the results will need to be updated and re-analyzed at suitable intervals in succeeding years. He cautioned that " results might change with time for some of these studies."

Wittes also noted that the findings of these trials apply only to patients whose cancer has spread to other parts of the body or those at higher risk of relapse because the cancer has spread to many nodes. In addition, the results may not apply to other high-dose regimens.

These limitations raise important questions about future directions of clinical research and recommendations for patient care. "We expect that there will be lively discussion, debate, and even disagreement among physicians about the implications of these findings," Wittes said. "Some may consider the matter settled, at least for these particular patient groups, and will no longer consider high-dose chemotherapy with transplants worthy of further testing. Others will be more impressed with the

limitations of the present trials and will be eager to continue studying different high-dose combinations."

NCI continues to support ongoing phase III studies of HDC/BMT in breast cancer, and it is possible that these may reveal an advantage for certain subsets of patients or for different high-dose regimens. For example, a national trial is now under way to test high-dose therapy in women who have only four to nine cancerous lymph nodes.

Another U.S. trial in women with 10 or more involved lymph nodes using a different high-dose regimen with transplant support has enrolled the required number of patients and results should become available in the next one to two years.

Many breast cancer patients currently receive high-dose therapy outside of trials. "Although particular circumstances may still lead physicians to recommend high-dose therapy for some patients, the NCI strongly encourages the use of well-designed clinical trials whenever possible," said Wittes. "Only in this way will we eliminate the uncertainties that continue to exist and improve outcomes for patients over today's standard treatment approaches."

Klausner also stressed the importance of participation in trials. "These five trials took nine years to yield these preliminary data because it took so long to enroll the required number of patients," he said. "Greater participation by physicians and patients in clinical trials would speed answers, not only to crucial questions concerning high-dose chemotherapy with transplants, but other cancer treatments as well."

It is important to note that HDC/BMT has been proven in clinical trials to be the most effective therapy in several other cancers, including certain kinds of leukemia and lymphoma. The results of the breast cancer trials do not apply to other kinds of cancer.

Summaries of the five studies and their findings are available on the ASCO Web site (http://www.asco.org). More detail will be available at the time of the presentations on May 17. Portions of the ASCO meeting, including these presentations, will be accessible through the organization's Web site.

More information is also available on the NCI's Web site for clinical trials (http://cancertrials.nci.nih.gov), including a questions and answers fact sheet on these studies.

For more information about cancer visit NCI's Web site for

patients, public, and the mass media at http://www.nci.nih.gov.

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:19-APR-1999 16:09:50.00

SUBJECT: Re: Additional meeting regarding religious perspectives

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

TEXT:
either day okay with me.
larry miike
-----Original Message-----
From: Meslin, Eric (OD) <MeslinE@od.nih.gov>
To: NBAC Members E-list <nbac-members@lists.Princeton.EDU>
Date: Monday, April 19, 1999 10:06 AM
Subject: Additional meeting regarding religious perspectives

>Commissioners--
>
>As you know we're trying to schedule a(nother) meeting within the next two
weeks
>to hear from religious thinkers regarding the stem cell project. The
meeting
>would be in Washington DC. Although we haven't finalized the date or
attendees
>we have to move quickly, so I'd like to know your availability on either
May 6
>or 7 for a one day meeting (perhaps not even a full day to allow you to
come in
>and out on the same day.)
>
>Eric
>
>
>
>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
>
>

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:19-APR-1999 16:42:17.00

SUBJECT: Re: Additional meeting regarding religious perspectives

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 not available on either May 6 or May 7 (and, by the way, from the west coast the notion of "in and out on the same day" doesn't apply to meetings in Washington DC!)
alex

On Mon, 19 Apr 1999, Meslin, Eric (OD) wrote:

> Commissioners--
>
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> to hear from religious thinkers regarding the stem cell project. The meeting
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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:19-APR-1999 16:07:00.00

SUBJECT: Additional meeting regarding religious perspectives

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

TEXT:
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to hear from religious thinkers regarding the stem cell project. The meeting
would be in Washington DC. Although we haven't finalized the date or attendees
we have to move quickly, so I'd like to know your availability on either May 6
or 7 for a one day meeting (perhaps not even a full day to allow you to come in
and out on the same day.)

Eric

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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

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:19-APR-1999 17:02:44.00

SUBJECT: RE: Additional meeting regarding religious perspectives

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 return from Beijing on the evening of the 5th, so I suppose I could come down to DC that night and be there for a meeting on the 6th--although I don't know how conscious I will be. We have a scheduled visitor at the Center on the 7th and I am very reluctant to have her change her plans.

Tom

-----Original Message-----
From: owner-nbac-members@lists.Princeton.EDU [mailto:owner-nbac-members@lists.Princeton.EDU]On Behalf Of Meslin, Eric (OD)
Sent: Monday, April 19, 1999 4:05 PM
To: NBAC Members E-list
Subject: Additional meeting regarding religious perspectives

Commissioners--

As you know we're trying to schedule a(nother) meeting within the next two weeks to hear from religious thinkers regarding the stem cell project. The meeting would be in Washington DC. Although we haven't finalized the date or attendees we have to move quickly, so I'd like to know your availability on either May 6 or 7 for a one day meeting (perhaps not even a full day to allow you to come in and out on the same day.)

Eric

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

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tim Leshan <TLESHAN@ascb.org> (Tim Leshan <TLESHAN@ascb.org> [UNKNOWN])

CREATION DATE/TIME:20-APR-1999 18:27:01.00

SUBJECT: Stem Cell Update

TO: Sbeck@researchamerica.org (Sbeck@researchamerica.org [UNKNOWN])
READ:UNKNOWN

TO: aeckerd@prodigy.net (aeckerd@prodigy.net [UNKNOWN])
READ:UNKNOWN

TO: jkatz@natlbcc.org (jkatz@natlbcc.org [UNKNOWN])
READ:UNKNOWN

TO: Jsalomon@mail.faseb.org (Jsalomon@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

TO: Skoppi@endo-society.org (Skoppi@endo-society.org [UNKNOWN])
READ:UNKNOWN

TO: stomlinson@bio.org (stomlinson@bio.org [UNKNOWN])
READ:UNKNOWN

TO: rlipner@basshowes.com (rlipner@basshowes.com [UNKNOWN])
READ:UNKNOWN

TO: Tim Leshan <TLESHAN@ascb.org> (Tim Leshan <TLESHAN@ascb.org> [UNKNOWN])
READ:UNKNOWN

TO: slrbc@aol.com (slrbc@aol.com [UNKNOWN])
READ:UNKNOWN

TO: Priscilla_Short@ama-assn.org (Priscilla_Short@ama-assn.org [UNKNOWN])
READ:UNKNOWN

TO: dperry@AGINGRESEARCH.ORG (dperry@AGINGRESEARCH.ORG [UNKNOWN])
READ:UNKNOWN

TO: KHendricks@aap.org (KHendricks@aap.org [UNKNOWN])
READ:UNKNOWN

TO: Acshipp@aamc.org (Acshipp@aamc.org [UNKNOWN])
READ:UNKNOWN

TO: mstephens@vsadc.com (mstephens@vsadc.com [UNKNOWN])
READ:UNKNOWN

TO: HarleyT@pva.org (HarleyT@pva.org [UNKNOWN])
READ:UNKNOWN

TO: wolpe@phrma.org (wolpe@phrma.org [UNKNOWN])
READ:UNKNOWN

TO: lsoler@jdfcure.org (lsoler@jdfcure.org [UNKNOWN])
READ:UNKNOWN

TO: ichow@faseb.org (ichow@faseb.org [UNKNOWN])
READ:UNKNOWN

TO: md@capitolassociates.com (md@capitolassociates.com [UNKNOWN])
READ:UNKNOWN

TO: schenault@basshowes.com (schenault@basshowes.com [UNKNOWN])
READ:UNKNOWN

TO: stipton@asrm.org (stipton@asrm.org [UNKNOWN])
READ:UNKNOWN

TO: EMARINCOLA@ascb.org (EMARINCOLA@ascb.org [UNKNOWN])
READ:UNKNOWN

TO: amp@amprogress.org (amp@amprogress.org [UNKNOWN])
READ:UNKNOWN

TO: pcatterall@AGINGRESEARCH.ORG (pcatterall@AGINGRESEARCH.ORG [UNKNOWN])
READ:UNKNOWN

TO: susan_quantius@aau.edu (susan_quantius@aau.edu [UNKNOWN])
READ:UNKNOWN

TO: Dbmoore@aamc.org (Dbmoore@aamc.org [UNKNOWN])
READ:UNKNOWN

TO: fpwhite@mail.faseb.org (fpwhite@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: rokelley@uic.edu (rokelley@uic.edu [UNKNOWN])
READ:UNKNOWN

CC: tzemlo@mail.faseb.org (tzemlo@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: nbradish@bio.org (nbradish@bio.org [UNKNOWN])
READ:UNKNOWN

CC: araanan@aps.faseb.org (araanan@aps.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: nwells@vsadc.com (nwells@vsadc.com [UNKNOWN])
READ:UNKNOWN

CC: hgarrison@mail.faseb.org (hgarrison@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: tlawless@faseb.org (tlawless@faseb.org [UNKNOWN])
READ:UNKNOWN

CC: bernstei@mail.faseb.org (bernstei@mail.faseb.org [UNKNOWN])
READ:UNKNOWN

CC: apendleton@anatomy.org (apendleton@anatomy.org [UNKNOWN])
READ:UNKNOWN

TEXT:
The last week has been an active one on the stem cell issue. Here is brief and rough update.

1. A few groups working on the stem cell issue met with Rep. Lowey (D-NY) and Rep. Leach's [R-IA) staff early last week. We had a very good discussion about where we stand on the Hill with this issue. We discussed the need to touch base with the House Appropriations Committee staff to get a sense of where they are on this issue. We all took assignments and will have gathered data by tomorrow.

2. The following day, many of the same groups and some others met with White House staff including Chris Jennings and Rachel Levinson. We were assured that the stem cell issue is a priority for the White House. We described our efforts to date with Congress and the plans we have for the future. Dan Perry of the Alliance for Aging Research said he was working with the patient groups to develop a message to be used in the media. When asked if the White House was considering a compromise on this issue we were told that they saw no need to at this point.

3. On the 14th at the National Health Council breakfast John Porter responded to a question about what he thought would happen with the stem cell issue. Porter said he does not want this issue to take away from the more important issue of funding for biomedical research. He expects and amendment on the Labor-HHS bill on this issue, but he is optimistic that even if it passes there that it won't in the Senate. Porter will support the NIH effort to fund stem cell research. I think we should follow Mr. Porter's advise namely that while we need to work this issue we need to remember the big picture.

4. At the Labor-HHS Hearing on Thursday Rep. Duke Cunningham [R-CA] announced publicly that he will support health research using pluripotent stem cells. He cited the long and arduous process he went through wrestling with the issue, the benefits and promise of the research, and noted that the decision may not necessarily be popular in his district. I view this as a good sign, but I don't want to read too much into it as far as other members.

5. NBAC met last week as well and further discussed the stem cell issue. I was not there, but I understand there was a good airing of both sides of the issue. They hope to have completed the "Science" chapter by the end of the month.

6. The NIH institutes have answered Senator Specter regarding his

question about how each of them could use stem cell research. I have a copy if you need it.

Next week on Tuesday, April 27 at Noon, Paul Berg, Ph.D., Cahill Professor in Cancer Research, Department of Biochemistry and Director of the Beckman Center for Molecular and Genetic Medicine at Stanford University School of Medicine will give a briefing on stem cell research to Congressional staff. The event will be held in Room 192 of the Senate Dirksen Office Building. Please let me know if you would like to attend. Please also let folks on the Hill know about this event. Thanks.

****

Tim Leshan
Director of Public Policy
American Society for Cell Biology
tleshan@ascb.org
www.jscpp.org/jscpp
301-530-7153 (p)
301-530-7139 (f)

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Rodrigues, Dennis (OD)" <RodriguD@OD31TM1.OD.NIH.GOV> ("Rodrigues, Dennis (OD)" <RodriguD@OD31TM1.OD.NIH.GOV> [UNKNOWN])

CREATION DATE/TIME:22-APR-1999 12:52:05.00

SUBJECT: FACT SHEET ON STEM CELL RESEARCH

TO: HHSPRESS@LIST.NIH.GOV (HHSPRESS@LIST.NIH.GOV [UNKNOWN])
READ:UNKNOWN

TEXT:
Note: Some recipients have been dropped due to syntax errors.Please refer to the "$AdditionalHeaders" item for the complete headers.
National Institutes of Health
Office of the Director

NEWS RELEASE

Wednesday, April 21, 1999
[Update to March 30, 1999 Fact Sheet]

FACT SHEET ON STEM CELL RESEARCH

The Department of Health and Human Services (DHHS) has determined that current law permits federal funds to be used for research utilizing human pluripotent stem cells. The National Institutes of Health (NIH) plans to move forward in a careful and deliberate fashion to develop rigorous guidelines that address the special ethical, legal, and social issues relevant to this research. The NIH will not fund research using human pluripotent stem cells until guidelines are developed and widely disseminated to the research community and an oversight process is in place.

THE PROMISE OF STEM CELL RESEARCH

Scientists have recently isolated and successfully cultured human pluripotent stem cells (1,2). These human pluripotent stem cells have an unlimited capacity to divide, and the ability to develop into most of the specialized cells or tissues in the body.

This advance represents a major step forward in human biology and has generated much enthusiasm and interest among scientists and the public, particularly patients and their families. Because these cells can give rise to many different types of cells, such as muscle cells, nerve cells, heart cells, blood cells, and others, they are enormously important to science and hold great promise for advances in health care. For example, further research

using pluripotent stem cells may help us:

--Generate cells and tissue that could be used for transplantation. Pluripotent stem cells may be stimulated to develop into many different specialized cells of the body, which may someday be used as replacement cells and tissue to treat many diseases and conditions including Parkinson's disease, spinal cord injury, stroke, burns, heart disease, diabetes, and arthritis.

--Improve our understanding of the complex events that occur during normal human development and also help us understand what goes wrong to cause diseases and conditions such as birth defects and cancer.

--Change the way we develop drugs and test them for safety and potential efficacy. New medications could be tested using human pluripotent stem cells, such as liver cells or skin cells; only the drugs which are both safe and appear to have a beneficial effect would graduate to human testing.

LEGAL ISSUES

These human pluripotent stem cells were isolated using two different methods. One group of scientists derived the pluripotent stem cells from early-stage embryos donated by people who were undergoing fertility treatment in an in vitro fertilization (IVF) clinic. Another group of scientists isolated the pluripotent stem cells from non-living fetuses obtained from pregnancies that had been terminated. In both cases, all of the individuals gave full informed consent for the embryos or fetal tissue to be used in research. Neither research project utilized federal funds. Because of the regenerative capacity of pluripotent stem cells, a single culture of human pluripotent stem cells could supply numerous other researchers.

Federal law currently prohibits the DHHS from funding human embryo research. In light of this legislative ban, the Director of the NIH sought a legal opinion from the DHHS Office of the General Counsel on whether DHHS funds may be used for research utilizing human pluripotent stem cells.

After a thorough analysis of the law, DHHS concluded that the congressional prohibition on the use of DHHS funds for certain types of human embryo research does not apply to research utilizing human pluripotent stem cells because such cells are not embryos. The legal opinion also clarified that human pluripotent stem cells derived from non-living fetuses would fall within the legal definition of human fetal tissue and are, therefore, subject to certain Federal restrictions on the use of such tissue.

Thus, research using pluripotent stem cells derived from human embryos can be funded by DHHS. Research that generates and uses pluripotent stem cells from non-living fetuses can also be supported by DHHS, subject to existing law and regulation.

NIH SUPPORT

In view of the scientific and medical benefits that may result from research using pluripotent stem cells, the NIH plans to fund research using these cells. It is essential that the Federal government play a role in funding and overseeing the conduct of this research, so that all scientists--both privately and federally funded--have the opportunity to pursue this important line of research. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of industry and academe.

The NIH understands and respects the compelling ethical, legal, and social issues relevant to pluripotent stem cell research and is sensitive to the need for stringent oversight of this research that goes beyond the traditional NIH scientific peer review process. In light of these issues, the NIH plans to move forward in a careful and deliberate way, prior to funding any research utilizing pluripotent stem cells.

In an effort to ensure that any research utilizing human pluripotent stem cells is appropriately and carefully conducted, the NIH convened a Working Group of the Advisory Committee to the Director (ACD), NIH to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells on April 8, 1999. The goal of the Working Group is to provide advice to the ACD about the scientific, ethical, legal, and social issues relevant to guidelines for the conduct of research utilizing human pluripotent stem cells. The working group met in public session. It is composed of scientists, patients and/or their families, ethicists, clinicians and lawyers. They were asked to consider advice from the National Bioethics Advisory Commission (NBAC), the public, and the Congress. As a result of the public discussion on April 8th, the Working Group is currently revising draft guidelines. Once developed, guidelines for research utilizing human pluripotent stem cells will be published in the Federal Register for public comment for 60 days. Until both the guidelines and the oversight process are in place, interested investigators have been notified, via the NIH web site, NIH program staff, and the Deputy Director for Intramural Research that they cannot use DHHS funds to conduct research using human pluripotent stem cells.

---

1 Michael Shamblott, et al, Derivation of pluripotent stem cells from cultured human primordial germ cells. "PNAS", 95: 13726-13731, Nov. 1998.

2 James Thomson, et al, Embryonic stem cell lines derived from human blastocysts. "Science", 282: 1145-1147, Nov. 6, 1998.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Scott-Jones, Diane " <dscott@nsf.gov> ("Scott-Jones, Diane " <dscott@nsf.gov> [UNKNOWN])

CREATION DATE/TIME:27-APR-1999 18:24:10.00

SUBJECT: RE: May 7 special meeting

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

TEXT:
Hi Eric,
I really regret that I cannot attend this meeting. I had hoped that you could hold it on Thursday. If there is any chance I can clear my schedule, I will come. Unfortunately, I have just returned from two back-to-back meetings, which is why I missed the Charlottesville meeting. I'm sure the discussion next Friday will be important for our work.
Cordially,
Diane
Diane Scott-Jones, Ph.D.
Program Director, Child Learning and Development
Division of Social, Behavioral, and Economic Research
4201 Wilson Blvd., Room 995
National Science Foundation, Arlington, VA 22230
Phone: 703-306-1732 Fax: 703-306-0485
http://www.nsf.gov/sbe/sber
Professor of Psychology, Temple University
Philadelphia PA 19122 215 204-1559

> -----Original Message-----
> From: Meslin, Eric (OD) [SMTP:MeslinE@od.nih.gov]
> Sent: Tuesday, April 27, 1999 4:04 PM
> To: NBAC Members E-list
> Subject: May 7 special meeting
>
> Dear Commissioners et al:
>
> We've finalized the additional meeting where a number of religious
> scholars will
> be presenting their views on stem cell research. The agenda, list of
> participants and other logistics information will be sent to all
> commissioners
> in the next day or so, even though all of you are not able to attend. If
> you
> were not planning to come and find that your schedule can be freed up,
> please
> let Margaret or Pat know asap. The meeting is intended to be a
> "conversation",
> not a discussion of drafts of the report. It is still an NBAC meeting
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> opportunities for public comment), but we'll set the room up with a
square
> circle table to enhance the feeling of discussion. Transcripts will be
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> I look forward to seeing some of you next week.
>
>
> Eric
>
> Eric M. Meslin, Ph.D
> Executive Director
> National Bioethics Advisory Commission
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> Tel: (301) 402-4242
> Fax: (301) 480-6900
> Email: MeslinE@OD.NIH.GOV
> http://www.bioethics.gov

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME:27-APR-1999 16:06:58.00

SUBJECT: May 7 special meeting

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

TEXT:
Dear Commissioners et al:

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Tel: (301) 402-4242
Fax: (301) 480-6900
Email: MeslinE@OD.NIH.GOV
http://www.bioethics.gov

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tim Leshan <TLESHAN@ascb.org> (Tim Leshan <TLESHAN@ascb.org> [UNKNOWN])

CREATION DATE/TIME:29-APR-1999 12:31:42.00

SUBJECT: Fwd: Recent events

TO: Ellen_Gadbois@labor.senate.gov (Ellen_Gadbois@labor.senate.gov [UNKNOWN])
READ:UNKNOWN

TEXT:
I thought you might be interested in this report I sent around to some of my colleagues regarding the Stem Cell briefing Paul Berg gave on Tuesday and the Nobel Laureate hearing yesterday.

Paul's briefing to Senate and House staff went very well. About 50 people attended to hear Paul give his scientific presentation. He began by describing how stem cells are formed and then discussed the various kinds of stem cells. He described how the cells are obtained and he discussed their potential for treating disease. Paul kept his talk short to leave plenty of time for Q&A. There were several good questions from staff. Staff present included Specter, Mack, Harkin, Hatch as well as House Commerce Committee and the Pro-life Caucus. I think Paul did a nice job of framing the debate, but sticking to the science in answering some tough questions such as, "won't it kill the embryo to extract the stem cells." To which he answered yes, but the embryo is not viable at this stage, and these embryos will ultimately go unused and then be discard. Making the point that if we are not able to use these embryos to obtain the stem cells they will go to waste any way. He also mentioned that the private sector was doing this work any way. I got the sense that the questions from those who oppose stem cell research were more of an attempt to find a compromise rather than to say this should not go forward no matter what. All in all I don't think he changed anyone's mind, but it was a good rational discussion about the issue and I think Paul answered questions that some of our supporters had.

I thought the Nobel hearing before Porter's subcommittee went well too. Members who were in attendance for at least some of the time included, Porter, Miller, Northrup, Hoyer and Pelosi. Paul Berg's testimony focused on the promise of the Genome and stem cell research. Joseph Goldstein of UT Southwestern in Dallas focused on the importance of clinical research and training of physician scientists. Thomas Cech of the University of Colorado, Boulder, discussed the importance of allowing for serendipity in basic research. His own research on a pond organism led to important work in cancer. Taking a some what different approach the last two panelist were young investigators: David Chang a MD/PhD. from UCLA and Ulrick Heberlain a professor of Anatomy at UCSF who is studying Drosophila and alcoholism. There was good discussion about a range of issues including, NIH funding, physician scientists, stem cell, FOIA, private sector research and regulatory burden. They were asked by Porter if

NIH could spend the increase. Of course the answer was yes, but they all said the most important thing was steady growth. Dr. Goldstein expanded on the physician scientists issue saying he thinks we are reaching a crisis in terms of lack of trained researchers in the clinic. Paul was asked several stem cell questions by Porter and Miller who seemed to want to get him on the record about the value of the research and the importance of the moral and ethical issues. Porter asked about the FOIA issue and how it could impact the research community. Cech gave the same arguments we have all been using to oppose the proposed reg. Miller and Northrup wanted to make the point that the private sector was doing a lot of research too. Paul was pretty down on the private sector and its willingness to share information. The group agreed that the profit factor made private research much different from that which is federally funded. Miller asked about the impact of regulatory burden on research. Cech described how it seems every time he does a grant there is another form to fill out and he half jokingly recommended that for every form created two should have to be eliminated. Miller liked that. Again a good day. Unfortunately the Kosovo debate was going on at the same time so many on the subcommittee did not attend. Please let me know if you have any questions.

Tim

****

Tim Leshan
Director of Public Policy
American Society for Cell Biology
tleshan@ascb.org
www.jscpp.org/jscpp
301-530-7153 (p)
301-530-7139 (f)

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: kathi hanna <khanna@chesapeake.net> (kathi hanna <khanna@chesapeake.net> [UNKNOWN])

CREATION DATE/TIME: 4-MAY-1999 09:14:17.00

SUBJECT: Geron announcement

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

TEXT:
Good Morning:

I saw on ABC news this morning that Geron Corp. is going to make an announcement today about a major acquisition that will allow them to combine the techniques of "somatic cell nuclear transfer, telomerase science, and pluripotent stem cell research" for clinical application. Staff will try to follow this but if any of you have information on this, please let me know.

Thanks,

Kathi

RECORD TYPE: FEDERAL (NOTES MAIL)

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

CREATION DATE/TIME: 6-MAY-1999 17:53:12.00

SUBJECT: Update

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

TEXT:
Dear Commissioners et al;

A couple of updates:

NBAC Meeting Involving Religious Scholars, May 7th

Below you'll find the agenda for the meeting tomorrow. Several commissioners will be making the trip to DC to hear testimony from a number of prominent scholars on the stem cell report. As with all commission meetings, there will be a public comment period, and the proceedings will be transcribed. In addition, we've arranged to have a rapporteur (one of Jim Childress' students from UVA) prepare a meeting summary. We'll try to make this available for the Chicago meeting next week; if not, Jim will give a verbal summary.

NBAC Chicago Meeting, May 11-12

Briefing books will be going out tomorrow. The agenda is limited to two items: HBM and Stem Cells. You'll be receiving a fair amount of reading. principally a number of background papers for the stem cell discussion.

HBM: It is Harold's intention to make substantial progress towards agreement on all of the recommendations, and to leave the meeting with relatively little additional work to be done (e.g., only aesthetic or minor editorial changes). Jim Childress has been hard at work on Chapter 4)Ethics), but due to a computer glitch we have to send it to you electronically over the weekend; we'll also ensure that a hard copy is available at the hotel when you check in on Monday, May 10. Chapter 5 will be sent by fax and electronically to you tomorrow, and

will be available at the meeting.

Stem Cell: Your briefing book will include a rough draft of the full report,
including a number of proposed draft recommendations. In addition you'll find
the latest drafts of commissioned papers, portions of which may be adapted for
inclusion in the body of the report itself.

Letter and Memo to the President: Adequacy of Federal Protections

Below you will find the text of the letter and memo Harold sent to the President
on Wednesday, with copies to the federal agencies today providing NBAC's
preliminary findings. You've seen an earlier version of this material. Please do
not distribute it yet; it is for your information. We will be making copies
available at the meeting next week, at which point it will become public. It
will also go to relevant members of Congress.

Eric

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30th MEETING
NATIONAL BIOETHICS ADVISORY COMMISSION

Religious Views on Research
Involving Human Embryonic Stem Cells

May 7, 1999
Riggs Library, Healy Hall
Georgetown University
37th and O Streets, NW
Washington, DC 20057
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TENTATIVE DRAFT AGENDA

Friday-May 7, 1999

8:30 am Opening Remarks

James F. Childress, Ph.D.

8:40 am Catholicism
Kevin W. Wildes, S.J., Ph.D., Georgetown University
Edmund D. Pellegrino, M.D., Georgetown University
Margaret Farley, Ph.D., Yale University

9:00 am Discussion with Commissioners

9:20 am Judaism
Rabbi Elliot N. Dorff, Ph.D., University of Judaism
Rabbi Moshe Tendler, Ph.D., Yeshiva University
Laurie Zoloth, Ph.D., San Francisco State University

9:50 am Discussion with Commissioners

10:10 am Break

10:25 am Eastern Orthodoxy
Demetrios Demopulos, Ph.D., Holy Trinity Greek Orthodox Church

10:35 am Discussion with Commissioners

10:55 am Islamic
Abdulaziz Sachedina, Ph.D., University of Virginia

11:05 am Discussion with Commissioners

11:25 am Protestantism
Gilbert C. Meilander, Jr., Ph.D., Valparaiso University
Nancy J. Duff, Ph.D., Princeton University Theological Seminary
Ronald Cole-Turner, M.Div., Ph.D., Pittsburgh Theological Seminary

11:55 am Discussion with Commissioners

12:15 pm Lunch

1:15 pm Public Comment

1:35 pm Discussion among Commissioners

2:15 pm Next Steps
James F. Childress, Ph.D.

2:30 pm Adjournment

The President
The White House
Washington, DC 20005

Dear Mr. President:

Consistent with your October 3, 1995, Executive Order 12975, the National Bioethics Advisory Commission has focused a good deal of its efforts over the last three years on issues surrounding the protection of human research subjects. I know of your interest, as well as that of the Congress, which has rightfully inquired about the adequacy of existing protections. To supplement the reports we have already submitted, I take this opportunity to provide you with a summary of our concerns and preliminary findings, some of which will, in our judgment, require further actions by the Federal Government. The attached memo provides additional details, but our key concerns are the following:

* Federal protections for persons serving as human research subjects do not yet extend to all Americans.

* Despite widespread implementation of federal regulations by those departments and agencies sponsoring substantial amounts of biomedical research, a number of departments and agencies who sponsor primarily non-biomedical research or little research overall have failed to implement these federal protections.

* Federal protections do not always include specific provisions for especially vulnerable populations of research subjects.

* Many federal agencies find the interpretation and implementation of the Common Rule confusing and/or unnecessarily burdensome.

* Federal protections are difficult to enforce and improve effectively throughout the Federal Government, in part because no single authority or office oversees research protections across all government agencies and departments.

* New techniques are needed to ensure implementation at the local level.

We will submit a more comprehensive report to you in the coming months, which will provide specific recommendations for changes in the federal system for protecting human subjects. Of course, as with all NBAC studies, we will continue to ensure that the public, the research community, and the agencies of the Federal Government have an opportunity participate in the report's

preparation.

Sincerely,

Harold T. Shapiro

NBAC Summary of Preliminary Findings:
Adequacy of Federal Protections for Human Subjects in Research

Extending Federal Protections for Human Research Subjects to All Americans

In 1997, President Clinton stated that "science must respect the dignity of every American. We must never allow our citizens to be unwitting guinea pigs in scientific experiments...." That same month, the National Bioethics Advisory Commission (NBAC) resolved, as a matter of ethical principle, that no person should be enrolled in research without the twin protections of informed consent and independent review of the research. NBAC notes with concern that this goal remains unmet.

In particular, the protections of the Federal Policy for the Protection of Human Subjects, also known as the Common Rule, do not extend to all Americans; the Common Rule applies only to subjects in research regulated by the Food and Drug Administration (FDA) or to subjects in research sponsored by some Federal departments and agencies. Among the Common Rule's most important protections are the requirements for informed consent by research subjects and for independent review of the research by a local Institutional Review Board (IRB). Despite the fact that many research institutions voluntarily apply the Common Rule-even to their privately financed research-there are other significant sectors of privately funded research that remain ungoverned either by State or Federal law.

NBAC finds that the absence of Federal jurisdiction over much privately funded research means that the U.S. government cannot know how many Americans currently are subjects in experiments, cannot influence how they have been recruited, cannot ensure that research subjects know and understand the risks they are undertaking, and cannot ascertain whether they have been harmed.

Not only does this prevent the Federal Government from protecting Americans enrolling in research, but it affects the Federal Government's ability to craft policies governing emerging technologies. While preparing its 1997 report Cloning Human Beings, for example, NBAC noted that the Common Rule's lack of jurisdiction over privately funded research made it impossible to rely on IRBs as the primary mechanism for protecting human subjects against inappropriate uses of those technologies.

Implementation of the Common Rule

Beginning in 1996, Federal departments and agencies responded to NBAC's request for information pursuant to Executive Order 12975. NBAC is pleased to report that agencies have responded to the Executive Order not only by reporting on their current protections, but by evaluating those protections and taking steps to strengthen them. Based on the agency reports and actions and on its own investigations and contracted studies, NBAC concludes that the Common Rule has significantly reduced, but not eliminated, the possibility for harm to human subjects. As a result, NBAC also concludes that there is a need for significant improvement, both to enforce Federal protections and to make their implementation less burdensome for Federal agencies and researchers.

Research regulated by the FDA or sponsored by one of the Federal departments or independent agencies that have adopted the Common Rule requires prior approval and continuing oversight by an IRB. NBAC has found that all the Federal departments and agencies that sponsor substantial amounts of biomedical research with human subjects have implemented these requirements. On the other hand, several departments and agencies that sponsor behavioral and other nonbiomedical research have not fully implemented the provisions of the Common Rule, despite the fact that such research may pose serious nonphysical risks, such as loss of insurance or employment, discrimination, incarceration, and invasion of privacy.

Although various Federal regulations do provide protections for certain vulnerable populations, these are not incorporated in the Common Rule. In addition, NBAC notes that the Common Rule does not require any special protections for especially vulnerable populations, such as children.

NBAC has identified occasions when nonbiomedical research that posed more than minimal risk was conducted on certain vulnerable populations; in some of these instances, the research was supported or conducted by one of the agencies that has not adopted additional protections, such as those found in Subparts B, C, or D of the Department of Health and Human Services regulations.

Federal departments and agencies do face obstacles in fully implementing the Common Rule. NBAC notes that many agencies find the Common Rule confusing or its provisions too burdensome in light of the type or amount of research they sponsor. Although some agencies have been taking steps to bring themselves into compliance with the Common Rule, nearly all of them agree that increased protection of human subjects cannot be achieved without additional staffing and highly visible statements of commitment from the leadership of their respective departments. Some also have suggested that a central authority governing human subjects research could help to interpret the Common Rule's requirements, create the oversight structures needed for its implementation, and advise on ethically complex protocols.

NBAC also finds that centralized leadership is needed to achieve consistent interpretation of key statutory and regulatory requirements. Lack of a single authority also means that improvement in human subjects protections, such as those specific to vulnerable populations, requires that every affected department independently adopt new regulations. This is inevitably slower and more inefficient than adoption by a central authority.

For example, in its 1998 report Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity, NBAC observed that some affected agencies were hard-pressed to reconcile their agency mission of fostering much-needed research into the causes and cures for mental illness with the shared Federal commitment to paying scrupulous attention to the interests of vulnerable human subjects. In addition, the absence of a single, authoritative Federal office to oversee human subjects protections will make it difficult to ensure that all affected departments will issue regulations implementing NBAC's

recommendations; indeed, similar recommendations were made 20 years ago by another national bioethics commission regarding the same population, but they were never adopted.

Ensuring Adequate and Accountable Local Oversight

The decentralized local system is sorely strained by inadequate staffing and education of IRBs; by the explosion in research activity; by emerging ethical issues arising from ethical issues raised by epidemiological and public health research; by the trend toward collaborative, multi-centered research; and by an absence of comprehensive public accountability.

NBAC's work highlights many of these problems and offers some solutions. Its upcoming report on research involving human biological materials, for example, suggests some solutions to the difficult problem of applying current Federal protections to epidemiological research on stored tissue, while its project on international research norms is revealing the dilemmas posed by collaborative research across national boundaries. Its report, Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity, emphasized the need to maintain the public's trust in the integrity of the scientific endeavor. To that end, NBAC suggested that "IRBs can effectively use the mechanisms of audit (both internal and external) and disclosure to improve accountability and inspire public confidence in their oversight activities."

Conclusion

NBAC finds that the current Federal regulations have served to prevent most recurrences of the gross abuses associated with biomedical research in the earlier part of this century. Nonetheless, some abuses still occur, and the system is in need of significant revision in order to provide clear, efficient, and authoritative guidance to Federal departments and agencies and to ensure that local oversight is effective and accountable to the public. This is essential to improving protections for human research subjects. It is also a necessary first step toward extending these protections to those Americans not

yet protected by any State or Federal standards for human subjects in research.