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ALTERNATIVE METHODS FOR DERIVING STEM CELLS

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

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CONTENTS

ALTERNATIVE METHODS FOR DERIVING STEM CELLS

TUESDAY, JULY 12, 2005

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:30 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter, Stevens, Harkin, and Murray.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning. This is the 16th hearing held by this subcommittee on this very important subject. When stem cells came upon the scene in November 1998, this subcommittee scheduled a hearing within 10 days thereafter, and has been pursuing this subject very, very diligently over the course of the intervening 7 years.

The ban on Federal funding for stem cell research has impeded the National Institutes of Health from pursuing this very important subject. Through the leadership of this subcommittee, the funding for NIH has been increased from $12 billion to $28 billion, providing very significant funding which could have been used for stem cell research but has not been because of the prohibition.

Now, there is grave concern that we are not moving far enough or fast enough on scientific research on the issues where stem cells could save lives. There is a battle between those who say that it is the destruction of human life, which I believe it is not. These stem cells are created—or these embryos are created for in vitro fertilization and those not used are discarded. There are some 400,000 now frozen, which will be discarded unless they are used.

This subcommittee again took the lead in appropriating some $1 million, which we are increasing this year to $2 million, to encourage adoption of embryos. If these embryos could be turned into life, none of us would advocate at all using them for scientific research. But when the option is to throw them away or use them, it seems at least to me, that it is a clear cut choice.

We expect to have the Senate take up a number of bills coming to the floor in the course of the next several days. They are not yet all written and we are trying to get copies of them. The principal piece of legislation is the House-passed bill, which is identical to legislation which Senator Harkin and I have introduced in the Sen-

ate. That will remove the restrictions so that the Federal funds can be used for stem cell research.

There is another promising approach, which we will be exploring in today's hearing, which is yet in the very, very early stages, which would be able preserve the embryo and still harvest the stem cells.

Again, subject to what these hearings produce and what the floor debate produces, if we can pass the House bill, Specter-Harkin, that is the most important bill to be enacted. If we can move ahead and enact other legislation which would hold the promise of preserving the embryos and still have stem cells harvesting, that is certainly worth exploring.

There is the so-called Bartlett bill coming out of the House, which may be on the Senate floor. We have not seen the full contours of that, but I am advised preliminarily that—that would maintain the ban which exists now to prohibit Federal funding. If that is so, I would be totally opposed to it.

Just one final word on a personal note. President Nixon declared war on cancer in 1970. When we devoted the resources to that war, which we have devoted to other wars, I think we would have found a cure for cancer by this time.

We all have very, very close personal experiences, some more personal than others, with members of our families or loved ones who have been stricken by the maladies where scientific research could have provided cures.

Carey Lackman, a member of the Senate family, who many of you knew, my chief of staff for many years, worked for Senator Heinz more than a decade ago, worked for me as chief of staff, died last year of breast cancer; a beautiful young woman of 48. She is really symbolic of so many women who have lost their lives from breast cancer. That could be replicated on prostate cancer. It could be replicated on heart disease and many, many other ailments where there is the potential to save lives.

As is well known from the terrible pictures which appear of me repeatedly in the press and on television, I have been a victim of identity theft. As I have said, from time to time, I look in the mirror every morning and cannot recognize who I am. But I cannot help thinking that had the Nixon war on cancer really been waged with intensity, that there would have been a cure, a preventative for Hodgkin's lymphoma cancer, with which I now am engaging in a fierce battle.

So, there is a very strong personal note to my own view. As has been reported, some 50 Republicans voted for the legislation in the House, because in many ways personal experiences—I hope we do not have to come to a point where 535 of us have personal experiences before we lead the battle for some 110 million Americans who suffer directly or indirectly from maladies which could be cured by the NIH research or perhaps by stem cells.

Let me turn now to the distinguished former chairman of the full committee, who himself—well, he may want to speak for himself about his own leadership on the scientific research and his work to combat prostate cancer.

Senator Stevens.

OPENING STATEMENT OF SENATOR TED STEVENS

Senator STEVENS. Thank you, Mr. Chairman, for holding the hearing today. I am sorry I will not be able to stay through it, as I have my Commerce hearing at 10 o'clock. But this is a topic of critical importance.

I do not think I know anyone who has not had some experience with cancer, personally or in the family. Mine was prostate cancer and I am pleased to say that so far I have survived that. I am very aware of your situation and admire your courage. So, I want to work with you in every way.

I have been a long-time supporter of medical research and particularly stem cell research. It is a means of developing new ways to treat and cure diseases like diabetes, and Parkinsons, or spinal cord injuries. Being the son of a father who went blind just right after I was born, I hope that someday stem cell research may lead to ways to make the blind capable of seeing.

I hope this hearing will explore new ways of tapping into potential stem cells, such as PGD, pre-implantation genetic diagnosis concept. These new means may not raise some of the ethical questions that haunted and hampered the progress of this research to date.

I want to stress that these new technologies should not come at the expense of proceeding full speed ahead with current research efforts on stem cells, using methods that are already proven to work. My scientist and research friends tell me that lines of stem cells approved for use were from federally funded research in 2001 are simply not sufficient and that many may have been contaminated.

I share your direct approach to stem cell research. I believe we should find some way to derive stem cell lines, and allow those lines to be developed, and used for federally funded research. We must do that now and not wait for new technology to develop. What is at stake is too important to put off.

So, I commend the scientists who are pioneering new ways to treat this disease through stem cell research and I want to thank all of you for being here today.

I will review the statements, Mr. Chairman. Thank you very much.

Senator SPECTER. Thank you, Senator Stevens.

I just want to officially note before turning to our first witness, I have a constituent in Pittsburgh whose name is Jim Cordy, and he suffers from Parkinson's. As we have heard testimony in this room, we are very close to a cure for Parkinson's.

Jim Cordy introduced me to the hourglass, which I now carry with me from time to time. It is a great photo op.

Every time I see Jim Cordy, he turns the hourglass upside-down and he says to me, "Arlen Specter, my life is drifting away, just as these sands are going through the hourglass. What are you doing about it?"

This subcommittee, and Senator Stevens, and Senator Harkin, and I have done a lot about it but we have not done enough about it. We are not going to rest until we find a cure for Parkinson's, until we find a cure for cancer. In a country which has a gross na-

tional product of $11 trillion, it is not enough to put one-fifth of 1 percent on medical research.

In a Federal budget of $2 trillion, $600 billion, it is not enough to put 1 percent into medical research. Health is number one. That is our major capital asset, and has languished for 7 years with the opportunities for stem cell research, which are languishing, not being taken care of, is just as scandalous and intolerable. I am glad that the leaders are bringing the matter to the floor so that we can move ahead and to save lives.

STATEMENT OF JAMES F. BATTEY, M.D., Ph.D., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS, AND CHAIR OF NIH STEM CELL TASK FORCE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator SPECTER. Dr. Battey, thank you for joining us today. Our first witness is Dr. James Battey, Director of the National Institute on Deafness and Other Communication Disorders of the NIH. He has his B.S. from California Institute of Technology, and M.D. and Ph.D. degrees from Stanford.

Dr. Battey has testified before this subcommittee on many occasions, and at one time for a while we were afraid of losing you, Dr. Battey. Senator Bettilou Taylor tells me that some of us might have been helpful in keeping you at NIH, which is great for the country, great for the world. The floor is yours.

Dr. BATTEY. Thank you very much, Senator. Also great for me, I might add. Thank you very much. It is a pleasure to be here again today to discuss with the subcommittee stem cell research.

As the committee understands very well, human embryonic stem cells have already proven to be a very valuable tool for advancing our knowledge about cell specialization, and they offer enormous potential to be medically valued.

However, using the established methods published by James Thomson in 1998, the only way to generate human embryonic stem cell lines is to remove the inner cell mass from a 5-day-old pre-implantation human blastocyst, which many feel is tantamount to destruction of human life.

There have been recent announcements about alternative ways to establish human pluripotent stem cells, which may share some of the magical properties of the cell lines that were established using the technique of Dr. Thomson. These methods claim to avoid the contentious issue of creating, destroying, or harming human embryos.

This past May, the President's Council on Bioethics published a white paper on "Alternative Sources of Human Pluripotent Stem Cells", and today I will focus my time with you on both describing these alternate methods and then giving a snapshot of the state of the science as we examine this issue today.

Doctors Landry and Zucker observed that, during the in vitro fertilization process, a number of the embryos stop dividing and are, therefore, unsuitable for implantation and are referred to as "dead" embryos. They have raised the possibility that it might be possible to harvest cells from these dead embryos and use them to create pluripotent stem cell lines. In fact, they put forward the notion that

this would be really no different than organ donation by a person who is judged to be brain dead.

From a scientific perspective, though, there is no published study that shows it is possible to generate an embryonic stem cell line from a dead embryo in rodents, non-human primates, or humans. Were such a cell line to be generated, one would have to look very carefully at the genetic content of those cells, because there was probably a reason why that embryo stopped dividing. That reason might compromise the value of a cell line derived from those cells, were there to be genetic abnormalities.

Representative Bartlett has reminded us that, during the pre-implantation genetic diagnosis process, there is a process whereby, before implanting the embryo, a genetic diagnosis is made to eliminate genetic disease from being a problem, a difficulty for the soon-to-be-born child. At the eight-cell stage, roughly 3 days into development, one of these eight cells, called the blastomere, is removed from that embryo.

Now the cells are still pluripotent at that point in time. What Representative Bartlett has proposed is that it might be possible to generate an embryonic stem cell line from this single blastomere that is removed from the embryo.

There were some studies in mice that suggest that this can work. At the current situation now, though, is it has not been demonstrated to work for either non-human primates or for humans. So, we do not know that it is possible to establish a cell line from a single cell. In fact, the closest that anyone has come is to establish a cell line from the morula stage, which is the fourth day of development, where there are somewhere between 10 and 30 pluripotent cells. Dr. Yuri Verlinski, in Chicago, has been able to generate a cell line at that stage.

Were we able to make cell lines, again, they would have to be checked very carefully for pluripotency, for the capacity to self-renew indefinitely, and all the other cardinal properties that make human embryonic stem cells the wonderful tool that they are for biomedical research and offer the promise for us to be able to someday generate populations of cells to replace cells that have been ravaged by diseases like Parkinson's disease or Type 1 diabetes.

Now William Hurlbut, who is with us today actually, and will describe his proposal in greater detail, has a concept called altered nuclear transfer. I think rather than dwell on this idea myself, I will let Dr. Hurlbut describe this to the committee himself, since it is his idea.

But what I will point out is that Dr. Hurlbut's method, although scientifically quite interesting, has yet to be proven in principle for the establishment of a human pluripotent stem cell line.

Finally, there is the issue of reprogramming the nucleus of a somatic cell. The developmental biology community was absolutely stunned in 1997 when Ian Wilmut cloned a sheep, the sheep Dolly, because that showed that it was possible to reverse the differentiation process, to turn it backwards. Many of us thought, until that event, that differentiation was a one-way street and that once you were differentiated; there was no way to go back.

Well, the cloning of Dolly proved that we were wrong. There is the capacity to turn the differentiation process in reverse. Were we

able to understand biochemically, all of the molecular basis for doing this, we would be able to take a cultured cell, de-differentiate it back to pluripotent state, and then differentiate it to become whatever cell type we might need to treat disease or disorder.

This is a wonderful possibility for the long-term future. But there are many, many basic science questions about the de-differentiation process that will need to be understood before we can move forward and utilize this technology to generate cells that are interesting for medical research.

So in closing, the NIH places a very high priority on support for research using all types of stem cells, and we are absolutely committed to supporting the development of a wide variety of methods to generate pluripotent cells that may be useful for basic translation and clinical studies.

PREPARED STATEMENT

But let me point out that the NIH would be nowhere in our effort to fund research involving pluripotent cells or all the rest of our nearly 40,000 grants and contracts without the remarkable generosity of this subcommittee, and specifically, without the unflagging support of Senators Specter and Harkin.

We remain extremely grateful to you for your continued support. I look forward to working with you for many years on this to advance all fields of biomedical research and would be happy to do my best to try to answer any questions the subcommittee might have at this time.

[The statement follows:]

PREPARED STATEMENT OF DR. JAMES F. BATTEY

Mr. Chairman, Senator Harkin, and Members of the Subcommittee, I am pleased to appear before you today to testify about stem cell research. Human embryonic stem cells (hESC) have proven to be an important tool for advancing our knowledge about cell specialization, and have great potential to be medically valuable. However, using established methods, these unique cells cannot be obtained without destroying human embryos. There have been recent announcements about alternative ways to establish human pluripotent stem cell lines that claim to avoid the contentious issues of creating, destroying or harming human embryos. This past May, the President's Council on Bioethics published a white paper on "Alternative Sources of Human Pluripotent Stem Cells." I am focusing my testimony on analysis of the methods highlighted in this report.

PLURIPOTENT STEM CELLS FROM DEAD EMBRYOS

Drs. Donald Landry and Howard Zucker at Columbia University College of Physicians and Surgeons noted that during the human in vitro fertilization (IVF) process, there are numerous embryos that fail to continue to divide, and are therefore judged to be unsuitable for implantation. These non-dividing entities are deemed to be "dead," and they propose that harvesting cells from these embryos for the purpose of creating a hESC line is no different than organ donation by a person judged to be "brain dead." They argue that this approach is morally acceptable.

From a scientific perspective, there is no published study showing that it is possible to generate an embryonic stem cell line from a non-dividing, "dead" embryo in rodents, non-human primates or humans. If stem cell lines could be derived from such embryos, the resulting cell line would have to be carefully checked for karyotypic (genetic) abnormalities or other defects, which may have been the underlying cause of the embryo's lack of development. This research will require that clear criteria be established to determine when a "non-dividing embryo" is dead.

Finally, the Dickey Amendment to the Department of Health and Human Services (DHHS) appropriations act prohibits the use of funds appropriated to DHHS to support the creation of a human embryo for research purposes or research in which a human embryo is destroyed, discarded, or subjected to risk of injury or death great-

er than that allowed under Federal requirements for fetuses in utero. Applicability of this prohibition would have to be analyzed before NIH could fund research on this technique using human embryos.

PLURIPOTENT STEM CELLS FROM BIOPSIED BLASTOMERES

This proposal, suggested by Representative Roscoe Bartlett (R-MD), involves creating an embryonic stem cell line by using a blastomere cell from an embryo. When performing pre-implantation genetic diagnosis (PGD), a single blastomere cell is removed from an 8-cell stage embryo (approximately Day 3 in embryo development where all cells are assumed to be totipotent) for genetic analysis, and the remaining seven cells constituting the embryo are used for reproductive purposes through the standard IVF procedure. The proponents of this proposal suggest that this is proof of principle that removal of a single cell does not frequently damage the remaining embryo. Using this premise, this proposal argues that a single cell, or several cells, might be removed from an embryo at the 8-cell stage at the same time the embryo is undergoing PGD and these additional cell(s) could be used for the purpose of creating a hESC line. The proposal further argues that if one limits this approach to embryos undergoing PGD, one is: (1) not compromising any embryos that are not already being compromised for PGD; and (2) assured the embryos being used were created only for reproductive purposes.

From a scientific perspective, NIH is not aware of any published scientific data that confirms the establishment of hESC lines from a single cell removed from an 8-cell stage embryo. We are aware of the published research of Dr. Yury Verlinsky at the Reproductive Genetics Institute in Chicago that showed that a hESC line can be derived by culturing a human morula-staged embryo (Reproductive BioMedicine Online, 2004 Vol. 9, No. 6, 623–629, Verlinsky, Strelchenko, et al). It is also worth noting, however, that in these experiments, the entire morula was plated and used to derive the hESC lines. The human morula is generally composed of 10–30 cells and is the stage (Day 4) that immediately precedes the formation of the blastocyst (Day 5). It is not known whether a hESC line can be created from a single cell or a few cells because these cells appear to require close contact with surrounding cells for survival and for maintenance of the pluripotent state. Even with the hESCs derived from the inner cell mass of the human blastocyst, the odds of starting a hESC line from a single cell are poor, perhaps one in 20 tries. Thus, the odds of being able to start with a single cell from an 8-cell or morula stage embryo are likely to be challenging.

NIH believes that such experiments might be pursued in animals, including non-human primates. Experiments in animal model systems could be conducted to determine whether it is possible to derive hESCs from a single cell of the 8-cell or morula stage embryo. To date, NIH is aware of only two published reports where scientists developed mouse stem cell lines from individual blastomeres. NIH also does not know whether these experiments have been tried and failed in other animals and/or humans and, therefore, have not been reported in the literature. NIH explored whether there have been any attempts to use single cells from the 8-cell or morula stage of an animal embryo to start embryonic stem cell lines by consulting with scientists that are currently conducting related embryo research. From these discussions, these scientists believe it is worth attempting experiments using a single cell from an early stage embryo or cells from a morula of a non-human primate to establish an embryonic stem cell line. If this approach is successful, the resulting stem cell lines would, of course, have to be validated for genetic stability, pluripotency, and unlimited self-renewal—all cardinal features of embryonic stem cell lines generated from blastocysts by culturing the inner cell mass.

NIH concludes that the possibility of establishing a hESC line from an 8-cell or morula stage embryo can only be determined with additional research. NIH would welcome the receipt of investigator-initiated grant applications on this topic using animal embryos. As with all grant applications, such proposals would be judged for scientific merit by peer review and then will be awarded research funds if sufficient funds are available.

Live births resulting from human embryos that undergo PGD and are subsequently implanted seem to suggest that this procedure does not harm the embryo; however, there are some reports that some embryos do not survive this procedure. In addition, long-term studies are needed to determine whether this procedure produces subtle injury to children born following PGD. This experiment in human embryos at either the morula or the blastocyst stage would require evaluations of not only normal birth but also unknown long-term risks to the person even into adulthood.

Moreover, there are a number of questions to be resolved with regard to the nature of the cells removed from the 8-cell stage embryo. If the cells removed at this stage are totipotent (and most scientists would agree they are), then it might be argued that these cells are themselves embryos, i.e., having the potential to undertake all of the life functions of the adult. It is possible, however, that one could put these cells in an environment in which they will not continue to develop and, under these conditions, they would no longer be embryos.

As with the Landry-Zucker proposal, applicability of the Dickey Amendment would have to be analyzed before NIH could fund research on human embryos.

PLURIPOTENT STEM CELLS FROM BIOLOGICAL ARTIFACTS

Dr. William Hurlbut at Stanford University asserts that it may be possible to do the following: (1) genetically modify a somatic cell in culture, either reversibly or irreversibly inactivating a gene essential for normal trophoblast function/development (which is required for embryo implantation and development of the placenta); (2) use this genetically modified somatic cell as the source of a nucleus and genome for somatic cell nuclear transfer (SCNT) into a human oocyte. Dr. Hurlbut refers to this method as Altered Nuclear Transfer (ANT); (3) allow this oocyte to proceed to develop into a blastocyst; and (4) attempt to generate a hESC line from the inner cell mass of the blastocyst. Dr. Hurlbut argues that since the entity generated by SCNT had no capacity to develop a trophectoderm (the embryonic cells which becomes the placenta and umbilical cord), it never had the capacity to develop into a fetus and ultimately a child; it is, therefore, not a human embryo. Dr. Hurlbut asserts that since this entity is not a human embryo, and its destruction at the blastocyst stage to generate a hESC line is morally acceptable. His opinion is currently under debate.

From a scientific perspective, Dr. Janet Rossant at Mount Sinai Hospital in Toronto has identified a gene essential for normal trophoblast development/function in a mouse model system. However, no one has demonstrated that it is possible to execute the sequence of steps proposed by Dr. Hurlbut and obtain a pluripotent, genetically stable stem cell line. Embryonic stem cell derivations would need to undergo pilot experiments, first in rodents and then in non-human primates, to prove that this approach has merit and is technically feasible. If created, the stem cell lines would, of course, have to be validated as authentic, with all the properties associated with self-renewing, pluripotent embryonic stem cell lines.

Dr. Hurlbut's proposed approach to deriving hESCs is dependent upon the widespread acceptance of his assertion that the genetically modified entity created using his procedure is not, in fact, a human embryo.

There are no limitations on any pilot studies performed in rodents or non-human primates. Limits of Federal funding of research for any extension of this approach to humans would require an analysis of the applicability of the Dickey Amendment.

PLURIPOTENT STEM CELLS BY REPROGRAMMING SOMATIC CELLS

This proposal involves reprogramming human somatic cells, perhaps with the aid of special cytoplasmic factors obtained from oocytes (or from pluripotent embryonic stem cells), so as to "dedifferentiate" them back into pluripotent stem cells. Crucial to this approach is discovering a way to reverse cell differentiation all the way back to pluripotency, but not further back to totipotency.

From a scientific perspective, it may be possible at some time in the future to culture populations of somatic cells in the laboratory and reverse their differentiating process, enabling them to become pluripotent. Scientists may also identify the molecules in cells such as embryonic stem cells that are responsible for maintaining cells in a pluripotent state and use these factors to dedifferentiate somatic cells. This proposal would raise ethical issues if the dedifferentiation process were to proceed too far and create a totipotent cell (a cloned human zygote). Research conducted with somatic cells can be conducted with appropriated funds since no human embryos are involved, unless the dedifferentiation process proceeds too far and results in the creation of a cell equivalent to a zygote.

CONCLUSION

Although some of these approaches may address interesting scientific questions and may even lead to new ways to derive stem cells, science works best when all available avenues can be pursued simultaneously.

NIH places a high priority on support for research using embryonic and non-embryonic stem cells that will also be useful for basic, translational, and clinical studies. The NIH is very grateful for your continued support. I look forward to working

with you to advance this and all fields of biomedical research. I will be happy to try to answer any questions that you and the Subcommittee might have.

Senator SPECTER. Thank you very much, Dr. Battey.

We have been joined by Senator Harkin.

Senator Stevens, would you care to ask a question or two? I would be delighted to defer to you before you go to your other hearing.

Senator STEVENS. No. I defer to you. I agree with you 100 percent.

Senator SPECTER. Okay. Now that I have Senator Stevens's general power of attorney, we can proceed.

I now turn to my partner for many years standing. We talk with pride about the seamless transfer of the gavel and working together on these important issues.

Senator Harkin.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Thank you, Mr. Chairman. Again, I apologize for being late. I got stuck in some traffic downtown. But I just want to echo what I just heard Senator Stevens say. I agree with you 100 percent. So, that makes two of us who agree with you 100 percent.

If you do not mind, Mr. Chairman, I would like to just make a short statement, if you do not mind.

Senator SPECTER. By all means. We will reserve the time for your opening statement and then we will proceed with the questioning of Dr. Battey.

Senator HARKIN. I really appreciate that. First of all, I want to thank you, Senator Specter, for all of your years of leadership on this subcommittee and especially in this field of biomedical research. I think I can say without any fear of contradiction or being corrected that no Senator—no one here in the entire Congress—I include the House, too, has devoted more time, more energy, more intellectual pursuit of supporting biomedical research in this country than Senator Arlen Specter of Pennsylvania. No one. It has just been a real privilege to have worked alongside of you and with you through all these years in support of your leadership in this area.

You and I held the first congressional hearing on stem cell research in December 1998. You were chairman. This is our 16th hearing on this topic; I suppose we will have some more. But today's hearing is focusing on alternative methods of deriving stem cells has suddenly become very popular around this town among other people who want to maintain current restrictions on stem cell research.

Under this method, scientists take a 2-day-old embryo. It has eight cells. They extract one, a blastomere. Maybe you have gone into that, Dr. Battey. I do not know. I am sorry I missed your opening statement. But then they stimulate that blastomere to begin dividing. Then after a few days, scientists can use it to derive stem cells.

The supposed advantage here is that the original embryo is not destroyed. First of all, I want to say I am intrigued by this method. I believe it is worth pursuing. But we need to be clear about one thing as we listen to today's testimony. There is only one reason

why this method has suddenly become so popular and being debated around. I noticed the article that was in the paper this morning, an op-ed piece by Leon Kass. Because I believe that there are some who want to use this approach to defeat H.R. 810, or our bill, the Specter-Harkin bill, from being enacted and passed by the Senate, which I believe it has the votes to do, because it has strong bipartisan support.

The strategy seems to be to convince senators that instead of supporting our bill, the Specter-Harkin bill, that we should pin all our hopes on this blastomere method or the so-called, quote, "ethical" alternatives. I think people figure some who want to stop this type of research, they figure if they can pull enough votes off of our bill, then they can stop us from getting the 60 votes that we need to stop a filibuster and pass it.

I would point out that we had 58 signatures on the letter and we got more that want to support it. So, we have the votes. I can respect that position if blastomere extraction showed as much promise as our current method for deriving stem cells. But so far, it does not.

The method we are discussing today has not been published in a single scientific journal. It has not been cleared through peer reviews. It has only been tried in mice. We are a long way from proving that it works in human embryos.

So there are a lot of problems we have with it, and Dr. Kass, in his article, mentioned it this morning. He said it is too early to know which of these approaches, these alternative approaches, will prove most successful; or whether some alternative approach will be superior. As the council noted, these proposals raised some ethical questions of their own.

Well, I am not going to read the whole article but he goes on to describe some of these other approaches. Then he says, at the end he says, "We could be hopeful that a technological solution to our moral dilemma might soon be found and that this divisive piece of our recent political history will soon come to an end. The senators will be given a chance this week to enact legislation to increase funding for alternative sources. They should not miss this timely and promising thing."

But the point is that I am all for these alternative sources. I am all for these alternative methods. Let us go ahead and pursue them. But we already know how to derive stem cells. That was first done by Dr. Thomson at the University of Wisconsin about 8 years ago, I believe, now. So, we know how to do that.

To the extent that these other alternative approaches might work, fine. Not as a substitute. Not as some way of stopping what we are about to do and stopping the derivation of stem cells from already existing embryos in in-vitro fertilization clinics.

So, I think that is really the difference here. Somewhat, I think, to use this as a way of slowing this down and stopping it. When Dr. Kass talked about a moral dilemma, I would point out; the vast majority of the American people are speaking out on this. Did you see the front page—or the front cover of the Parade magazine this Sunday? A whole National Geographic issue.

I would point this out. Parade magazine, stem cell research. If you would open it up, they had a poll that they took, American peo-

ple, right here; 58 percent strongly favor this research on embryonic stem cells. Only 18 percent—well, 29 percent oppose somewhat or strongly oppose it.

So, I would just say to Dr. Kass one thing, I do not believe there is a moral dilemma here. Any kind of medical research of this nature is always going to have its detractors. We have been through this time and time and time again in the past.

There are those who—let us face it. There are those today who believe that any form of artificial birth control is morally unacceptable. There are those who believe that oral contraceptives are morally unacceptable. There are those who believe using condoms today is morally unacceptable. But the vast majority of the American people do not believe that way.

I give full license to those that have their own moral qualms about anything, but they should not impose their views on the vast majority of the American people who want us to pursue this course of action. That is what we are about. That is what Senator Specter has been the leader on all these years and what he is leading us on now.

So, I just wanted to make that strong opening statement and I thank you for your indulgence, Mr. Chairman, because it is not about either/or. It is about pursuing all of these basic research things that you have let us on for all these years. If we are going to fund these alternative approaches, that is fine, but do not stop the process that we have right now of deriving embryonic stem cells that have so much promise for cures faster than going down the road of these alternative approaches. With that, Mr. Chairman, I thank you for this time.

Senator SPECTER. Thank you very much, Senator Harkin. The proposition which you suggest on pursuing all the lines, I think is a very sensible one. You quote this morning's op-ed piece as saying we do not know—Dr. Kass does not know which would be the most fruitful, which suggests we ought to proceed on all lines.

But we will have to examine the legislation very carefully to make sure there is not a provision, which I understand there may be in one or more of these bills, which would preclude the Castle-DeGette bill and the Specter-Harkin bill from moving forward.

I was asked yesterday why I am having a hearing to explore alternatives which might produce some stopping of fundamental legislation which we have in mind. The object is to find out as much as we can, have a—see where we are and to see how much promise there is. If it is possible to preserve the embryo and harvest the cells, fine. But if it is very speculative and we have a bird in hand, let us not avoid going forward with what we know will work.

Dr. Battey, you have already referenced the fact that there are others who are going to be—you have deferred to them on some of the alternatives. I think the hearing would be best accommodated if we call them to the witness table today, and we hear their opening statements, and then have an interchange among you high-powered scientists, if we may.

So if Dr. Lanza, Dr. Green, Dr. Daley, and Dr. Hurlbut would step forward, we will proceed.

Our next witness will be Dr. Robert Lanza, Vice President, Medical and Scientific Development of Advanced Cell Technology, and

adjunct professor of surgical scientists at Wake Forest University School of Medicine, B.A. and M.D. degrees from the University of Pennsylvania. Thank you for joining us, Dr. Lanza, and we look forward to your testimony.

STATEMENT OF ROBERT LANZA, M.D., VICE PRESIDENT, MEDICAL AND SCIENTIFIC DEVELOPMENT, ADVANCED CELL TECHNOLOGY

Dr. LANZA. Thank you. Good morning, Mr. Chairman and distinguished members of the committee. My name is Robert Lanza, and I am the medical director at Advanced Cell Technology, a stem cell company in the emerging field of regenerative medicine. I am also adjunct professor at the Institute of Regenerative Medicine at Wake Forest University.

Regenerative medicine is accelerating its pace with many scientific groups worldwide, conducting research in preclinical tests of stem cells. International teams are beginning to pull away from researchers in the United States, given the current limitations of Federal funding of stem cell research.

Access to funding for developing new ways of isolating stem cells will not only help address current ethical concerns but will help the United States maintain its leadership position in medical research.

The most basic objection to stem cell research is rooted in the fact that embryos are deprived of their fundamental potential to develop to complete human beings. To date, there have been no reports of stem cells derived using an approach that does not destroy embryos.

The President's Bio-Ethic Council, chaired by Leon Kass, has outlined four approaches for creating stem cells without destruction of embryos. The first approach is to generate stem cells using a biopsy similar to pre-implantation genetic diagnosis. PGD involves removal of one or two cells, called blastomeres, from an embryo to test for diseases such as cystic fibrosis.

The procedure is relatively simple and is carried out routinely at IBF clinics worldwide. Using this approach, we have found that biopsied mouse embryos develop to term without a reduction in the developmental capacity. We have successfully isolated stem cells from single blastomeres, which demonstrated the ability to differentiate into derivatives of all three germ layers of the body, passing all of the tests associated with human embryonic stem cells.

The Kass report raises two ethical concerns regarding this approach. The first objection is that the biopsy could adversely affect the embryo. We propose a simple solution. Use only blastomeres from embryos undergoing routine PGD. Experts estimate that 1,000 healthy infants are born every year from embryos that have undergone PGD, a number significant enough to generate numerous new stem cell lines.

Another objection in the Kass report is that the biopsy cell could have the potential to develop into an embryo. In fact, human blastomeres have never been shown to have the capacity to generate viable embryos, and there is an increasing body of scientific knowledge suggesting that the cells in morula stage embryos, the 8 to 16 stage, have already committed to either becoming ICM cells

or trophectoderm. That only totipotent cell is the fertilized egg in the first four or so cells produced by its cleavage.

The blastomere approach does not involve the destruction of an embryo nor could the biopsy itself ever develop into an embryo. Eventually, we hope this method can be used to increase the number of lines that qualify for Federal funding and, at the same time, avoid some of the challenges associated with other methods in the Kass report.

For instance, one approach favored by many uses cloning to sabotage the development of embryos. Supporters claim that the "bundle of cells" that results is not an embryo. As a medical scientist, I think it is an abuse of science to use cloning and genetic manipulation to deliberately create crippled embryos, especially when these manipulations are not carried out for any scientific reason but rather to solve theological problems.

Let us be honest. A human embryo is a human embryo whether or not this or that gene is knocked out. It is hard to believe that human ensoulment depends on the expression of CBX–2. The blastomere approach uses a technique that already exists and would not require taxpayer funding to develop human cloning techniques.

The Kass report proposes two additional approaches. One is to deprive cells from embryos that are technically dead. However, we are talking about tiny clusters of cells, and you cannot take an EEG to determine if there is a loss of brain function. I have seen numerous human embryos stop dividing; fooling the embryologist into thinking they are dead. Then after a resting period, they go on to generate blastocysts. Unfortunately, the only way to know if an embryo is dead is if the cells are dead.

The final approach, known as de-differentiation, does not require human eggs or embryos. This is an exciting concept and involves taking an adult cell and reprogramming it back to adult—to pluripotent stem cells. We and other groups have already generated some exciting data on this but it is still very preliminary and requires further research. This approach has few, if any, ethical objections.

Given the data to date further investigations of the cell biopsy and de-differentiation approaches should be funded to determine if stem cells can be derived in humans. We believe that a commitment of $15 million to $20 million would significantly accelerate this research and its likely success in the future.

The hope of these approaches described here today, we hope that this will result in the expansion of stem cell lines available for therapies. However, until these approaches are perfected in humans, it is important to emphasize the urgent need to continue access to surplus IBF embryos. It is for this research. Again, I cannot emphasize enough that the approaches that I am describing here are complementary to S. 471 and H.R. 810.

PREPARED STATEMENT

While you were listening to this testimony, another 10 Americans have died of diseases that could potentially be treated using stem cells in the future. It would be tragic not to pursue all the

options and methods available to us to get this technology to the bedside as soon as possible.

[The statement follows:]

PREPARED TESTIMONY OF DR. ROBERT LANZA

Good morning, Mr. Chairman and distinguished members of the committee. My name is Robert

Lanza and I am the medical director at Advanced Cell Technology, a stem cell company in the emerging field of regenerative medicine. I am also Adjunct Professor at the Institute of Regenerative Medicine at Wake Forest University School of Medicine.

The field of regenerative medicine is accelerating its pace of progress with many scientific groups worldwide conducting research and preclinical tests of human stem cell lines, and beginning to draw up timetables for clinical development. International teams are beginning to pull away from the researchers in the United States given the current limitations on Federal funding for stem cell research. Access to Federal funding for developing new ways of isolating pluripotent stem cells will not only help address current ethical concerns, but will help the United States maintain its leadership position in medical research.

The most basic objection to embryonic stem cell research is rooted in the fact that ES-cell derivation deprives embryos of their potential to develop into complete human beings. To date, there have been no reports in the literature of stem cell lines derived using an approach that does not require destruction of embryos. The President's Bioethics Council chaired by Leon Kass has outlined four approaches for creating stem cells without the destruction of embryos.

The first approach would be to generate stem cells using an embryo biopsy similar to preimplantation genetic diagnosis. "PGD" involves removal of one or two cells called "blastomeres" from an embryo to test for genetic diseases like cystic fibrosis. The procedure is relatively simple and is carried out routinely in IVF clinics worldwide. The ability to generate stem cells using this method could circumvent the ethical concerns voiced by many. Using this approach, we have found biopsied mouse embryos developed to term without a reduction in their developmental capacity. We successfully isolated stem cell lines from single blastomeres, which demonstrated the ability to readily differentiate into derivatives of all three germ layers of the body, passing all the tests generally associated with human ES cells (publication pending).

The Kass report raises two ethical concerns regarding this approach. The first objection is that the biopsy could adversely affect the embryo. We propose a simple solution—use only blastomeres from embryos undergoing routine PGD. Experts estimate that a thousand healthy infants are born every year from embryos that have undergone PGD—a number sufficient to generate numerous new stem cell lines.

Another objection in the Kass report is that the biopsied cell could have the potential to develop into an embryo. In fact, human blastomeres have never been shown to have the capacity to create viable embryos in the laboratory, and there is an increasing body of scientific evidence suggesting that the cells in morula-stage embryos (8–16 cells) have already committed to becoming either ICM cells or trophectoderm. At a minimum, it is clear that some degree of differentiation has occurred, and there is an increasing consensus that the only "totipotent" cells are the fertilized egg and the first 4-or-so cells produced by its cleavage.

The blastomere approach does not involve the destruction of an embryo, nor could the biopsied cell ever develop into an embryo. Eventually, we hope this method can be used to increase the number of stem cell lines that qualify for Federal funding, and at the same time, avoid the challenges associated with other methods outlined in the Kass report. For instance, an approach favored by many, and first proposed by ACT years ago, uses cloning to sabotage the development of embryos. Supporters claim the "bundle of cells" is not an embryo and could be used to ethically generate stem cells. As a medical scientist, I think it is an abuse of science to use cloning and genetic manipulation to deliberately create crippled human embryos, especially when these manipulations are not carried out for any medical or scientific reason, but rather to address theological problems. Let's be honest, a human embryo is a human embryo whether or not this or that gene is knocked out. It's hard to believe that human ensoulment depends on the expression of cdx2. The blastomere-approach uses a technique that already exists, and would not require taxpayer funding to further develop human cloning techniques.

The Kass report also proposes two other approaches. One is to derive stem cells from "technically dead" embryos. However, we're talking about tiny clusters of cells;

you can't take an EEG to determine if there's loss of brain function. I've seen numerous human embryos stop dividing, fooling the embryologist into thinking they're no longer viable; then, after a significant "resting" period, they go on to generate intact blastocysts. Unfortunately, the only sure way to know if an embryo is dead is if the cells are dead.

The final approach, known as dedifferentiation, doesn't require human eggs or embryos. This is an exciting concept, and involves taking an adult cell and reprogramming it back into a stem cell in the laboratory. We and several other groups have already generated some exciting data on this, but it's still preliminary and requires further basic research. This approach holds great promise and there are few, if any ethical concerns.

Given the our research to date and the data generated from animal models, further investigations of the single-cell biopsy and dedifferentiation approaches should be funded and encouraged to determine if stem cells can be derived in humans. We believe that a significant commitment of Federal funding of $15 to $20 million would significantly accelerate this research and its likely success within this decade.

We hope the approaches described here today will successfully result in the future expansion of stem cell lines available for human therapies. However, until these approaches are perfected in humans, it is important to emphasize the urgent need for continued access to surplus IVF embryos that would otherwise be discarded. It is for this that I commend the sponsors of Senate

Bill 471, and applaud you for your commitment to supporting ES cell research and the advancement of regenerative medicine.

While you were listening to this testimony, another 10 Americans have died of diseases that could potentially be treated using stem cells in the future. It would be tragic not to pursue all the options and methods available to us to get this technology to the bedside as soon as possible.

Senator SPECTER. Thank you very much, Dr. Lanza.

We turn now to Dr. Ronald Green, Director of Dartmouth Institute of Study and Applied Professional Ethics. He currently heads the Ethics Advisory Board of Advanced Cell Technology. A graduate of Brown, a Ph.D. in religious ethics from Harvard. A member of the Human Embryo Research Panel, NIH, a Blue Ribbon Commission. Appointed to recommend policy for Federal funding on pre-implantation of human embryo. Thank you for coming to Washington today, Dr. Green, and we look forward to your testimony.

STATEMENT OF RONALD M. GREEN, DIRECTOR, ETHICS INSTITUTE, DARTMOUTH COLLEGE

Dr. GREEN. Thank you very much for having me here, Senator Specter. As we meet today and this morning, only 22 embryonic stem cell lines are available for federally funded research. This is far too small a number for effective research. Furthermore, as has been said, all of these lines are of limited clinical value because they are contaminated with mouse proteins or viruses that are likely to cause rejection or new human diseases.

In the past year, four proposals have been put forward to find technical ways around this problem. One advocates the use of organismically dead embryos for stem cell derivation. A second argues for the use of altered nuclear transfer to produce developmentally incompetent embryos for the same purpose. Both of these proposals have been sharply criticized as involving the deliberate infliction of injury on early embryos. I substantially agree with these criticisms.

A third approach involves the reprogramming of body cells so as to restore them to the pluripotency typical of embryonic stem cells. While this approach is ethically unobjectionable, it is well beyond current scientific capabilities; although, research in this direction should be supported.

A fourth approach, and the one on which I want to dwell this morning, involves the use of single-cell blastomere biopsy. This procedure has already been well described by others this morning and I believe the technical detail is there. Because this approach does not involve the destruction of an embryo, if it could be applied to the creation of a human embryonic stem cell line, it could eliminate many of the ethical and legal objections to Federal support for embryonic stem cell research. So this is an approach with promise.

Nevertheless, serious ethical and legal questions remain. It has not yet been scientifically established that blastomere extraction is harmless to the embryo and prospective child. As such, this research may subject a born child to unknown risks in order to develop a stem cell line of use to others.

It might be argued that the child could benefit by having a line of stem cells made available for its future health care needs. But until research resolves the safety questions, this procedure cannot ethically be used on healthy embryos. I would add, I believe it cannot be used under current human subject's regulations as well.

However, single-cell biopsy for stem cell derivation could possibly be conducted ethically and legally at present, in conjunction with a pre-implantation genetic diagnosis, PGD procedure. The risks here of removing a cell could be ethically justified by the benefits to the prospective child of avoiding a genetic disease.

The use of any cells harvested in this procedure would be as ethically acceptable as the use of cells removed from an infant during a routine genetic diagnostic procedure. Nevertheless, although single-cell blastomere biopsy is an ethically promising way of deriving stem cell lines, it should not be regarded as an alternative to current methods that use embryos remaining from infertility procedures.

There are at least two reasons why I say this. First, it has not been demonstrated that embryonic stem cell lines can successfully be derived in this way. Placing all our hopes for stem cell development on this technology is not prudent. Nor is it fair to the many people awaiting cures through stem cell research.

Second, single-cell biopsy raises ethical questions of its own. As I have indicated, because of unknown risks it cannot ethically be used to derive stem cells from health embryos. Although this technology could be used in the course of legal analysis might conclude that Federal law prohibits funding for research on stem cell lines derived from PGD.

PREPARED STATEMENT

The most responsible government action at this time would be to support further research on single-cell blastomere biopsy, to establish its safety and efficacy while moving ahead on proven methods of expanding the number of stem cell lines available to researchers. Thank you.

Senator SPECTER. Thank you very much, Dr. Green, for tackling a very complex subject and making it, if not almost understandable, perhaps understandable.

Dr. GREEN. Thank you.

[The statement follows:]

PREPARED STATEMENT OF RONALD M. GREEN

Good morning, Mr. Chairman and distinguished members of the committee. My name is Ronald M. Green. I am a professor in the Department of Religion at Dartmouth College and Director of the Dartmouth's Ethics Institute. I also serve, in a pro bono capacity, as chairman of the Ethics Advisory Board for Advanced Cell Technology in Worcester, Massachusetts.

U.S. law currently prohibits the use of federal funds for "research in which a human embryo or embryos are destroyed."[1] On August 9, 2001, President Bush issued an executive order permitting funding for research on human embryonic stem lines established before that date. As of today, there are only 23 embryonic stem cell lines available for federally funded research. All of these lines are contaminated with mouse proteins and viruses that are likely to cause rejection or new human diseases.[2] There are also too few approved cell lines to provide adequate genetic diversity for much stem cell research and clinical care.[3]

In the past year, four proposals have been put forward to find technical ways around this impasse. All four proposals are presented and discussed in a White Paper issued by the President's Council on Bioethics.[4] One proposal advocates the use of "organismically dead" embryos for stem cell derivation.[5] A second proposes to use what is called "altered nuclear transfer" to produce developmentally incompetent embryos for the same purpose.[6] Both of these approaches have been sharply criticized by commentators inside and outside the President's Bioethics Council as possibly involving the deliberate infliction of injury on early embryos.[7][8][9]

A third approach involves the reprogramming or de-differentiation of differentiated somatic cells so as to restore them to the pluripotency typical of embryonic stem cells. While ethically unobjectionable, this approach is well beyond current scientific capabilities.

A fourth approach, and the one on which I want to dwell, involves the use of single-cell blastomere biopsy. This procedure is widely used in the process of preimplantation genetic diagnosis (PGD) as a way of testing for genetic disorders before the embryo is transferred to a womb. Hundred of PGD procedures have been performed in this country. The extraction of a single cell from the embryo at this stage does not appear to harm it or reduce its developmental potential. If this method could be applied to the extraction of a single cell for the creation of a human embryonic stem cell line, it could circumvent many of the ethical and legal objections to federal support for embryonic stem cell research.

Nevertheless, ethical and legal questions remain. It has not yet been scientifically established beyond a reasonable doubt that blastomere extraction is harmless to the embryo and prospective child. As such, this research may subject a born child to unknown risks in order to develop a cell line of possible use to others. It could be argued that the child might benefit by having a line of stem cells produce for its future health care needs. But until future research resolves these safety questions and proves that this approach is innocuous, it is doubtful whether parents could responsibly exercise proxy consent in this case or that institutional review boards could accept their consent.

The same problem arises when we ask whether such research could be permitted for federal support under current laws and regulations that prohibit research on an embryo or fetus that is not to its benefit and that involves greater than minimal risk.[10] Although banking a line of stem cells is arguably to the embryo's benefit, it

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[1] Dickey-Wicker Amendment. Public Law 104–99, Section 128, January 26, 1996, 110 Stat 34.

[2] J. Ebert, Nature Online, 24 January 2005. http://www.nature.com/news/2005/050124/pf/050124-1_pf.html

[3] Guidelines for Human Embryonic Stem Cell Research. National Academy of Sciences, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council. Washington, D.C.: National Academies Press, 2005.

[4] President's Council on Bioethics. "Alternative Sources of Pluripotent Stem Cells: A White Paper." Washington, D.C. May 2005.

[5] Landry, D. W. and H. A. Zucker, "Embryonic death and the creation of human embryonic stem cells," The Journal of Clinical Investigation 114 (2004), 1184–1186.

[6] W. Hurlbut, President's Bioethics Council, Meeting Transcript, December 4, 2004. http://www.bioethics.gov/transcripts/dec04/dec3full.html.

[7] J. Rowley, "Personal Statement of Dr. Rowley." Pp. 89–90 in "President's Council on Bioethics. "Alternative Sources of Pluripotent Stem Cells: A White Paper."

[8] Comments by J. Hanson and R. Doerflinger, President's Bioethics Council, Meeting Transcript, December 4, 2004.

[9] D. A. Melton, G. Q. Daley, and C. G. Jennings, "Altered nuclear transfer in stem-cell research—a flawed proposal." New England Journal of Medicine 351;27 (2004), 2791–2792.

[10] 45 CFR § 46.208(a)(2).

cannot be said with confidence at this time that removing a blastomere from an early embryo is to its net benefit or that it involves only minimal risk. It will take additional research, which might be supported by federal funding, to determine the level of risk to embryos associated with single-cell blastomere biopsy.

However, if single-cell biopsy for stem cell derivation proves technically feasible, it could possibly be conducted ethically and legally at present within the context of PGD. The risks here could be ethically justified by the benefits to the prospective child of avoiding a genetic disease. Use of any blastomeres harvested in the procedure would be as ethically acceptable as the use of tissue removed from a child during an ordinary surgical procedure. Some of the blastomeres made available in this way would be from genetically unaffected embryos and could be cultured for testing and for stem cell derivation for transplant purposes. Blastomeres from affected embryos might be developed into stem cell lines that could be used in the study of the family's genetic disease condition.

Would research on stem cell lines derived from blastomeres taken from embryos during PGD qualify for federal funding? This question will require further legal analysis, but there are reasons to believe that the research could qualify. Blastomere extraction does not destroy the embryo. PGD is a legitimate medical procedure widely used as a way of avoiding the birth of a child with a serious genetic disease. Even many of those who morally oppose PGD might agree that so long as the procedure is being conducted, it is morally permissible to use embryonic tissues remaining from it. In terms of the requirement prohibiting anything greater than minimal risk unless the research benefits the embryo, it could be argued that PGD "benefits" each embryo by affording it at least a chance of being born. In the absence of PGD, couples that carry disease-causing genes might entirely avoid trying to have biologically related children.

If it could be successfully developed, therefore, single-cell blastomere biopsy offers a way of resolving our current ethical and legal debates about the moral acceptability of human embryonic stem cell research. It would permit many of those who believe that human life begins at fertilization to support the derivation of new stem cell lines without compromising their core ethical beliefs.

Nevertheless, although single-cell blastomere biopsy is an ethically attractive way of deriving stem cell lines, it should not be regarded as an alternative to current methods that use embryos remaining from infertility procedures, an approach that many citizens regard as ethically acceptable. There are at least two reasons why this is so. First, it has not been demonstrated that embryonic stem cell lines can routinely and successfully be derived in this way. Placing all our hopes for stem cell development on this technology is not prudent, nor is it fair to the many people awaiting cures through stem cell research.

Second, single-cell biopsy raises ethical questions of its own. As I have indicated, it currently cannot ethically be used to derive stem cells where healthy embryos are involved, since the absence of risks to the resulting children has not yet been sufficiently demonstrated. Although this technology can be used in the context of PGD without adding additional risks, some people object to PGD itself. In addition, further legal analysis might lead to the conclusion that the Dickey Amendment prohibits federal funding for research on stem cell lines derived from PGD.

The most responsible governmental action at this time would be to support further research on single-cell blastomere biopsy to establish its efficacy and safety while moving ahead on proven methods of expanding the numbers of stem cell lines available to researchers.

Senator SPECTER. We now turn to Dr. George Daley, Associate Director of the Stem Cell Program at Boston Children's Hospital, and a member of the Executive Committee of the Harvard Stem Cell Institute. Dr. Daley received his bachelor's degree and M.D. from Harvard and a Ph.D. in biology from MIT. We appreciate you being here, Dr. Daley, and the floor is yours.

STATEMENT OF GEORGE Q. DALEY, M.D., Ph.D., ASSOCIATE DIRECTOR, STEM CELL PROGRAM, BOSTON CHILDREN'S HOSPITAL

Dr. DALEY. Thank you, Senator Specter, members of the committee. Thank you for inviting me to testify. My name is George Daley. I am here today representing the American Society for Cell Biology, which is a professional society of nearly 12,000 basic bio-

medical researchers here in the United States and throughout the world.

I am an associate professor at Boston Children's Hospital Harvard Medical School, and president-elect of the International Society for Stem Cell Research. My research is focused on using embryonic stem cells and adult stem cells to develop new treatments for leukemia and genetic diseases of the blood, like sickle cell anemia.

I am also clinically active at the Children's Hospital, where I see first hand the pain and suffering inflicted by these conditions on children and their families. My career is dedicated to making a difference in their lives through research and patient care.

I am here today to state my strong support for Senate passage of the Specter-Harkin version of H.R. 810, which has already passed the House of Representatives with broad bipartisan support. H.R. 810 would ensure that scientists can use Federal grant funds to study the wide range of valuable human embryonic stem cells that have been created since August 9, 2001, the date that President Bush announced his restrictive stem cell research policy.

H.R. 810 would expand research opportunities and accelerate progress towards newer and better therapies for the many children that currently not treat successfully. I am also here to give scientific perspective on several proposed alternatives for deriving human pluripotent stem cells that have been considered recently by the President's Council on Bioethics, and which are the subject of this hearing today.

I want to state at the outset that I support efforts to derive pluripotent cells by methods that would be ethically acceptable to all but I do not support delaying the pursuit of medical research on existing human ESL cell lines while these more speculative methods are tested. I believe that Senate passage of H.R. 810 is the surest means of supporting stem cell research at this juncture.

First, let me illustrate how human embryonic stem cells offer unique opportunities for research and create an imperative that the Federal Government provides expanded support. Critics of embryonic stem cell research are fond of saying that adult stem cells have been used to cure dozens of diseases while embryonic stem cells have helped no one.

I would like to challenge this claim. In essentially all cases of adult stem cell therapy, we are really talking about transplanting blood stem cells to treat leukemia, lymphoma, and genetic disease. Although bone marrow transplant has cured many lives, this form of adult stem cell therapy is not a certain cure. Even after many decades of clinical experience, bone marrow transplant remains an aggressive and toxic therapy that carries the highest mortality rate of any medical procedure that is routinely performed.

Indeed, I have cared for many patients who have died during this treatment. All of us working in hematology today agree that additional research is required. My laboratory is studying human embryonic stem cells in hopes of making blood stem cell transplants safer and more widely applicable. A critical part of this strategy is using somatic cell nuclear transfer that generates stem cells that are customized to the specific patients I mentioned earlier, kids with leukemia, immune deficiency, and sickle cell anemia.

We hope to correct the genetic defects in these patients, direct their differentiation of the cells into blood, and transplant kids with the genetically matched otology cells. This strategy is working in mice and we are eager to translate the work into humans but the current Federal funding policies have held us back.

Although it is true that no one to date has been treated with cellular therapies based on human embryonic stem cells, I can assure you that mouse embryonic stem cells have had a major impact on medical research. Over the past 25 years, mouse embryonic stem cells have been used to create models for scores of human diseases including cancer, heart disease, obesity, and Alzheimer's.

Research discoveries based on these models have lead to new drug development and, therefore, touched countless lives. As for the criticism that no one has been cured with embryonic stem cells, the field of human ESL research is a mere 7 years old, so it is premature to expect successful cell therapies to have already been delivered.

I believe it is only a matter of time before human ESLs are used in drug development research and become the basis for important new drug therapies and cell therapies in a wide array of diseases.

As further evidence of how human ESLs enable unique opportunities to study disease, consider research on Fanconi's anemia. Kids with Fanconi's anemia suffer bone marrow failure and often develop leukemia. Scientists have tried to model this disease in mice but the mice did not develop critical features of the human disease.

Recently, a team from the Reproductive Genetics Institute of Chicago isolated a human ESL line that carries a Fanconi's mutation and would enable us to study the uniquely human aspects of this disease. However, because of the current presidential policy, we cannot study these cells. To date, we have been unable to generate a Fanconi's model using presidential cell lines, and by this direct example, the President's policy is hindering our research.

Let me now turn to the several new proposals for making pluripotent ESLs that are designed to avoid the destruction of a human embryo. I want to point out that these so-called alternatives are not true alternatives, as they currently represent only speculative ideas for research that might or might not yield new stem cell lines and are fraught with their own ethical problems.

In most of these cases, the experiments needed to establish feasibility of these proposals would require research on human embryos, which would currently be prohibited under the Federal law by the Dickey amendment. Far preferable to spending limited research dollars on these speculative proposals, in my opinion, is support for research on additional embryonic stem cell lines that are available today, lines that are similar to those already approved under the Bush policy.

Senate passage of H.R. 810 would advance research that we know works, research where the ethical dilemmas have been understood and accepted by most.

Now among the speculative methods under discussion, the first involves extracting stem cells from embryos that are considered dead, because they have stopped dividing and will not develop further. If individual cells remain alive, they might be used to initiate stem cell lines.

The President's Council has found this strategy ethically sound and scientifically feasible, and so endorsed it. However, everything I know about deriving stem cells, tells me that to generate pluripotent cells from these defective embryos is likely to be far less efficient than IBF embryos. Even if cell lines can be generated, I imagine scientists will remain suspicious that they are abnormal and have questionable clinical utility.

Senator SPECTER. Dr. Daley, do you have much more of your prepared statement?

Dr. DALEY. I just have about a minute more.

Senator SPECTER. Proceed, then.

Dr. DALEY. The second method derives from pre-implantation genetic diagnosis, which we have already heard about. However, the biopsy procedure raises all sorts of ethical concerns and has, indeed, been dismissed as unacceptable during the initial inquiries of the council. Additionally, these first two methods did not produce genetically matched embryonic stem cells for patients.

This third method we will hear about from Dr. Hurlbut involves altered nuclear transfer. Such a strategy is technically feasible but in a piece written for the New England Journal of Medicine, my colleagues and I have rejected the concept as flawed.

Let me quickly summarize by saying that I do support the fourth speculative proposal, which is to derive pluripotent cells via direct de-differentiation of somatic cells to an embryonic stem cell life state, using chemical treatments or cell culture manipulation alone.

The President's Council found merit in this proposal but also raised the technically thorny issue of how to rule out whether a totipotent and, therefore, morally significant cell might be created by this procedure. In my view, the last two proposals, altered nuclear transfer and de-differentiation, raise a curious and challenging question. Can we assign moral value to a human cell; say a reprogrammed skin cell, based solely on its particular pattern of gene expression? Can humanity really be diagnosed in a single cell?

Finally, let me summarize that science cannot define when in the gradual course of human development we have deserved to be accorded individual and autonomous rights. I do not agree with the premise that the single cell zygote or any cell like it produced by nuclear transfer should be given the same considerations as living persons, and I do not view the embryo live in a practical world of choices, a world in which disease is a grim reality. Unless we want to turn back the clock and outlaw in vitro fertilization, then we as a society have already accepted that many more embryos are created than will ever become children.

PREPARED STATEMENT

I feel it is morally justified for patients to derive benefit from these embryos through medical research instead of relegating them to medical waste. Unless we are willing to argue the biological absurdity that our humanity can be reduced to a particular signature of gene expression, that exists when we reprogram skin cells through nuclear transfer, then we must support embryonic stem cell research in all its forms, which are vitally important and available to medical researchers today.

[The statement follows:]

PREPARED STATEMENT OF GEORGE Q. DALEY

Senator Specter, members of the Committee, thank you for inviting me to testify before you. My name is George Daley. I am here today representing the American Society for Cell Biology, a professional society of nearly 12,000 basic biomedical researchers in the United States and 50 nations around the world. I am Associate Professor of Pediatrics and Biological Chemistry at Boston Children's Hospital and Harvard Medical School, the Associate Director of the Stem Cell Program at Children's Hospital, a member of the Executive Committee of the Harvard Stem Cell Institute, and Board Member and President-elect of the International Society for Stem Cell Research (term to begin June 2007). My research is focused on using embryonic stem cells and adult stem cells to study blood development, and to develop new treatments for leukemia, and genetic diseases like immune deficiency, sickle cell anemia, thalassemia, and Fanconi's anemia. I am also clinically active as a hematologist at Children's Hospital, where I see first-hand the pain and suffering inflicted by these diseases on children and their families. My career is dedicated to making a difference in their lives through research and patient care.

I am here today to state my strong support for Senate passage of H.R. 810, which has already passed the House of Representatives by an impressive and bipartisan margin. H.R. 810 would ensure that scientists can use Federal grant funds to study the wide range of valuable human embryonic stem cell lines that have been created since August 9, 2001, the date that President Bush announced his restrictive stem cell research policy. H.R. 810 would expand research opportunities and accelerate progress towards newer and better therapies for the many children I currently cannot treat successfully.

I am also here to give scientific perspective on the several additional strategies proposed for deriving human pluripotent stem cells that have been considered recently by the President's Council on Bioethics, and which are the subject of this hearing today. I want to state at the outset that I support efforts to derive pluripotent stem cells by methods that would be ethically acceptable to all, but I do not support delaying the pursuit of medical research on existing human embryonic stem cell lines while these more speculative methods are tested. I believe that Senate passage of H.R. 810 is the surest means of supporting stem cell research at this juncture.

First let me emphasize why research on human embryonic stem cells is so vitally important, and why alternative forms of adult stem cell research cannot substitute for the study of embryonic stem cells.

Critics of embryonic stem cell research are fond of saying that adult stem cells have been used to cure dozens of diseases while embryonic stem cells have helped no one. I would like to examine that claim. In essentially all cases adult stem cell therapy really means transplantation of blood stem cells to treat leukemia, lymphoma, and various genetic diseases of the blood. Although bone marrow transplants have saved many lives, bone marrow transplant is never a certain cure. Even after many decades of clinical experience, bone marrow transplant remains an aggressive and toxic therapy that carries the highest mortality rate of any medical procedure that is routinely performed. For patients whose only bone marrow match is from unrelated donors outside the family, the treatment itself claims the lives of ~30 percent of patients in the first year. Indeed, I have cared for many patients who have died during treatment. All of us working in hematology today agree that additional research is needed.

My laboratory is studying embryonic stem cells in hopes of making blood stem cell transplants safer and more widely applicable. A critical part of the strategy is using somatic cell nuclear transfer to generate stem cells that are customized to the specific patients I mentioned earlier, kids with leukemia, immune deficiency, and sickle cell anemia. We hope to correct the genetic defects in these patient-specific cells, direct their differentiation into blood, and transplant kids with these genetically matched autologous cells. This strategy is already working in mice, and we are eager to translate this work into humans. The current Federal funding policies have held us back.

Although it is true that no one has to date been treated with cellular therapies based on human embryonic stem cells, I can assure you that mouse embryonic stem cells have had a major impact on medical research. Over the past 25 years, mouse embryonic stem cells have been used to create models for scores of human diseases, including cancer, heart disease, obesity, and Alzheimer's. Research discoveries based on these models has led to new drug development and therefore touched countless lives. As for the criticism that no one has been cured with embryonic stem cells, the field of human embryonic stem cell research is a mere 7 years old, so it is premature to expect successful cell therapies to have already been delivered to patients.

I believe it is only a matter of time before human embryonic stem cells are used in drug development research and become the basis for important new cell therapies.

As further evidence of how human embryonic stem cells enable unique opportunities to study disease, consider research on Fanconi's anemia. Kids with Fanconi's anemia suffer bone marrow failure, and often develop leukemia. Scientists have tried to model this disease in mice, but the mice do not develop bone marrow failure, and the adult blood stem cells from Fanconi's patients cannot be maintained in culture. Recently, a team from the Reproductive Genetics Institute of Chicago isolated a human embryonic stem cell line that carries a Fanconi's gene mutation. This cell line could enable us to study the uniquely human aspects of Fanconi's anemia. However, because of the current Presidential policy, we cannot study these cells with our Federal grant dollars. Thus my lab has been left to attempt to generate a Fanconi's model in one of our Presidential stem cell lines, which has proven to be far more cumbersome than simply obtaining the cells from Chicago. To date, we have not succeeded. By this direct example, the President's policy is hindering our research on this terrible childhood disease. Senate passage of H.R. 810 would make available Federal funds to perform this important medical research. [I have written about the "missed opportunities" for human embryonic stem cell research under the current Presidential policies, and wish to introduce this article into the record.[1]]

Let me now turn to the several proposed new methods for making pluripotent human stem cells that are designed to avoid the destruction of a human embryo. These so-called "alternatives" are not TRUE alternatives, as they currently represent only speculative proposals for research that might yield new stem cell lines, and are fraught with their own ethical problems. In most of these cases, the experiments needed to establish feasibility of these proposals would require research on human embryos, and thus would be prohibited under current Federal law by the Dickey amendment. Far preferable to spending limited research dollars on these speculative proposals, in my opinion, is support for research on additional embryonic stem cell lines that are available today—lines that are similar to those already approved under the Bush policy. Senate passage of H.R. 810 would advance research that we know works, research where the ethical dilemmas have been understood and accepted by most.

Among the speculative methods under discussion, the first involves extracting stem cells from embryos that could be considered "dead", because they have stopped dividing and will not develop further. If individual cells remain alive (and hopefully normal), they might be used to initiate lines of stem cells. The President's Council found this strategy ethically sound and scientifically feasible and so endorsed it. However, I anticipate that attempts to generate pluripotent cells from these defective embryos will be far less efficient than from excess IVF embryos. Even if cell lines can be generated, I imagine scientists will remain suspicious that they are abnormal and might lead to erroneous conclusions in research.

The second speculative method derives from pre-implantation genetic diagnosis, or PGD, in which one or two cells are removed from an early embryo and analyzed to diagnose serious inherited diseases like Sickle Cell Anemia. PGD insures that only embryos found free of gene defects are transferred to the woman so that she may have a healthy child. The suggestion has been made that biopsied cells might be used to produce pluripotent stem cell lines, and this would be ethically acceptable if the embryo remained unharmed. Dr. Lanza is here to represent his as yet unpublished success in using this strategy to produce pluripotent stem cell lines from mouse embryos. However, the biopsy procedure raises all sorts of ethical concerns and indeed has been dismissed as unacceptable during the initial inquiries of the President's Council. [Those who equate the zygote to a human being would reject the use of embryo biopsy because it removes cells at a stage when they might be considered developmentally equivalent to the zygote—that is, totipotent. Removing a totipotent blastomere is then the moral equivalent of producing a twin, which, in the view of opponents of embryonic stem cell research could not then be sacrificed for research. Embryo biopsy for stem cell research entails risks to embryos that are wanted for making a baby, rather than destined to be discarded as medical waste. If my wife and I carried a genetic disease we would accept the risk of the embryo biopsy procedure to insure we could have the healthiest child possible, but if we were simply infertile and using IVF to assist us in reproduction, we would not consent to having our healthy embryos biopsied; we would chose instead to donate our excess embryos to stem cell research. Dr. Lanza may suggest that lines be derived only from embryos already being biopsied for PGD, but the more cells one biopsies

[1] Daley, G.Q. Missed opportunities in embryonic stem-cell research. N Engl J Med 351, 627–8 (2004).

to accommodate both PGD and stem cell derivations, the greater the risk for embryo loss. As a practical and scientific matter, embryo biopsy for derivation of pluripotent cell lines is an unacceptable option.]

The third speculative method involves deriving pluripotent stem cells from something the President's Council has termed "biological artifacts". The best described of this procedure is called "Altered Nuclear Transfer", which entails introducing a genetic defect into a somatic donor cell prior to nuclear transfer, so that a disordered embryo results that can be a source of pluripotent stem cells but cannot develop into a human. According to Dr. Hurlbut, the method's chief proponent, what is produced would "lack the essential attributes and capacities of a human embryo", a biological artifact whose destruction to produce pluripotent stem cells would be ethically justified. Such a strategy is technically feasible but in a piece written for the New England Journal of Medicine, my colleagues and I have rejected this concept as flawed.[2] In reasoning echoed by the President's Council, we questioned whether the planned creation of what amounts to a defective embryo would silence ethical objections.

A more recent proposal put forth by Markus Grompe is a variation on Altered Nuclear Transfer called Oocyte Assisted Reprogramming, (OAR). Grompe also suggests altering the input somatic cell so as to preclude formation of a viable human embryo. He proposes using a gene like nanog, which might promote reprogramming of the donor somatic cell directly to something that resembles an embryonic stem cell, which is pluripotent, and avoids generating a cell like a zygote, which is totipotent—that is, able to divide on its own and form a viable human blastocyst. Scientifically, this idea is a reasonable hypothesis that must be tested and might or might not work. But even if this strategy works in mice, there is no guarantee it will work in humans, and verification would then require the creation and destruction of many manipulated human embryos, which might or might not have the altered characteristics that would make this method ethically "acceptable". If it works, I am concerned that in order to use Federal dollars for research US Scientists will be relegated to less-efficient processes like Altered Nuclear Transfer, while Korean scientists employ superior techniques.

The fourth speculative approach is to derive pluripotent cells via direct de-differentiation of somatic cells to an embryonic stem cell-like state using chemical treatments or cell culture manipulation alone. The President's Council found merit in this fourth proposal, but also raised the technically thorny issue of how to rule out whether a totipotent and therefore morally significant cell might be created by this procedure. In my view, these last two proposals raise a curious and challenging question: can we distinguish the moral value of a human cell based on its particular gene expression pattern? Can humanity really be diagnosed at the level of a single cell?

From my view, this last approach has scientific merit. We know cellular de-differentiation is possible; indeed, that is precisely what we do when we perform somatic cell nuclear transfer and reprogram a somatic cell back to a zygote. The Federal Government is already funding research into such cellular reprogramming. Indeed, last year I was one of nine recipients of the inaugural Pioneer Award from the Director of the National Institutes of Health to support highly innovative (that is, speculative) research of exactly this type. Although this strategy is worth pursuing, it is extremely high-risk, and may take years to perfect, and may never work as well as nuclear transfer, which we know we can practice today.

Research on each of these proposed strategies is at present untested in human cells, but if judged to be meritorious by the peer review process, should be funded. However, the already proven routes to obtaining embryonic stem cells from excess IVF embryos or through the use of somatic cell nuclear transfer should not be put on hold pending the outcomes of the more speculative methods.

Finally, let me emphasize that research on embryonic stem cells and embryo research in general is not solely about making tissues for transplantation to treat disease. Although the promise of new therapies is perhaps the most compelling reason to support expanded access to embryonic stem cells for research, I stress that it is equally important to pursue research that addresses fundamental questions about the earliest stages of human development. We know that a variety of birth defects can be traced to abnormal cell divisions during the first few days of life, and that infertility and miscarriage can also be traced to defects in the early embryo. We cannot learn everything there is to learn about these human disease conditions from studying animals. We must study the unique aspects of human embryo biology di-

[2] Melton, D.A., Daley, G.Q. & Jennings, C.G. Altered nuclear transfer in stem-cell research—a flawed proposal. N Engl J Med 351, 2791–2 (2004).

rectly, and the Federal government should support this vitally important basic research.

Science certainly cannot define when in the gradual course of human development we deserve individual and autonomous rights. I do not agree with the premise that the single celled zygote should be given the same considerations as living persons and I do not view the embryo as a human being, particularly when it is frozen in a freezer. As a physician and as a scientist and as a father I live in a practical world of choices, and a world in which disease is a grim reality. Unless we want to turn back the clock, and outlaw in vitro fertilization, then we as a society have already accepted that many more embryos are created than will ever become children. I feel it is morally justified to derive benefit from these embryos through medical research instead of relegating them to medical waste. And unless we are willing to argue the biological absurdity that our humanity can be defined by a particular signature of gene expression that exists in the totipotent cells of the early human embryo, then we must support the vitally important applications of embryonic stem cells to medical research.

Senator SPECTER. Thank you very much, Dr. Daley.

Our final witness on this panel is Dr. William Hurlbut, physician and consulting professor of the program in human biology at Stanford. After receiving his undergraduate and medical training at Stanford, he completed post-doctoral studies in theology and medical ethics. In addition to teaching at Stanford, he currently serves on the President's Council on Bioethics.

Thank you for coming to Washington today, Dr. Hurlbut and the floor is yours.

STATEMENT OF WILLIAM B. HURLBUT, M.D., PROGRAM IN HUMAN BIOLOGY, STANFORD UNIVERSITY

Dr. HURLBUT. Thank you. It is an honor to be here. I want to say that I speak for myself, not for the President's Council as a whole. I want to say from the onset that I agree with Senator Specter on the moral imperative of biomedical research and the scandal of priorities in our consumer culture.

It is clear to me that both sides of this difficult debate are defending important human goods, and both of these goods opening avenues for advance in biomedical science and preserving the fundamental moral principles on which our society is based are important to all of us.

In 1999, President Clinton's National Bioethics Advisory Commission issued a report entitled, "Ethical Issues in Human Stem Cell Research," acknowledging that a week-old human embryo is a form of human life that deserves respect. The Commission stated, "In our judgment, the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research."

Two months ago, the President's Council on Bioethics issued a white paper, entitled, "Alternative Sources of Pluripotent Stem Cells," which discusses such less morally problematic alternatives. After analyzing the scientific feasibility, practicality, and moral acceptability of a range of approaches, the Council endorsed for preliminary animal studies three proposals for the production of pluripotent stem cells, the functional equivalents of embryonic stem cells.

One of these proposals, altered nuclear transfer, is a broad concept with a range of possible approaches worthy of exploration. Altered nuclear transfer would draw on the basic techniques of so-

matic cell nuclear transfer, popularly known as therapeutic cloning, but with an alteration, such that pluripotent cells are produced without the creation and destruction of human embryos.

In standard nuclear transfer, the cell nucleus is removed from an adult body cell and then transferred into an egg cell that first has its own nucleus removed. The egg then has a full set of DNA, after the somatic cell nucleus is put into it, and then after electrical stimulation starts to divide like a naturally fertilized egg. This, of course, is how Dolly the sheep was produced. Altered nuclear transfer, used as the technology of nuclear transfer but with a preemptive alteration that assures that no embryo is created.

The adult body cell nucleuses, or the cytoplasm of the egg, that is the egg contents, or both, are first altered before the adult body cell nucleus is transferred into the egg. The alterations caused the adult body cell DNA to function in such a way that no embryo is generated but pluripotent stem cells are produced.

There may be many ways altered nuclear transfer can be used to accomplish this same end. One recent variation on this proposal, called oocyte assisted reprogramming, has been put forward by Markus Grompe, Director of the Stem Cell Center at Oregon Health Sciences University. In this variation of altered nuclear transfer, alterations of the nucleus of the adult body cell and the enucleated egg's contents before nuclear transfer would force early expression of genes characteristic of a later and more specialized cell type that is capable of producing pluripotent stem cells. Such a creation from its very beginning would never have the actual configuration or potential for development that characterizes a human embryo, and would, therefore, not have the moral standing of a human being.

As described in a recent op-ed in the Wall Street Journal, and documented in a joint statement posted at the Ethics and Public Policy Center web site, this proposal has drawn encouragement from leading scientists and wide endorsement from moral philosophers and religious authorities.

Altered nuclear transfer, in its many variations, could provide a uniquely flexible tool and has many positive advantages that would help advance embryonic stem cell research. Unlike the use of embryos from IDF clinics, altered nuclear transfer would produce an unlimited range of genetic types for the study of disease, drug testing, and possibly generation of therapeutically useful cells.

By allowing controlled and reproducible experiments, altered nuclear transfer would provide a tool for a wide range of useful studies of gene expression, imprinting, and inter-cellular communication. Furthermore, the basic research essential to establishing the technique would advance our understanding of developmental biology and might serve as a bridge to transcendent technologies, such as direct reprogramming of adult cells.

Moreover, as a direct laboratory technique, altered nuclear transfer with unburdened embryonic stem cell research from the additional ethical concerns of the so-called leftover IBF embryos, including the attendant clinical and legal complexities in this realm of great personal and social sensitivity.

I have discussed this proposal with leading molecular and cell biologists, and the general response is that altered nuclear transfer

is technically feasible, might be rapidly developed. Most scientists agree that in 12 to 24 months we would have a very good idea and maybe get there. Furthermore, this technique would not burden stem cell research with excessive costs or inconvenience.

The present conflict over the moral status of the human embryo reflects deep differences in our basic convictions and is unlikely to be resolved through deliberation or debate. Yet a purely political solution will leave our country bitterly divided, eroding the social support and sense of noble purpose that is essential for the public funding of biomedical science.

In offering a third option, altered nuclear transfer, defines with clarity and precision the boundaries that our moral principles are seeking to preserve while opening fully the promising possibilities of embryonic stem cell research.

Senator SPECTER. Dr. Hurlbut, are you about finished with your opening statement?

Dr. HURLBUT. About 30 seconds.

Senator SPECTER. Fine.

Dr. HURLBUT. As described by my colleagues, altered nuclear transfer is just one of a range of hopeful proposals. Specific legislation to support exploration and development of these complementary ways of obtaining pluripotent stem cells would greatly encourage this research. I want to say, I would favor a stand-alone bill, unencumbered.

As we enter the coming era of rapid advance in biotechnology, this kind of legislation would set a positive precedent for maintaining constructive ethical dialogue and encouraging creative use of our scientific knowledge. In recognizing the important values being defended by both sides of our difficult national debate over embryonic stem cell research, this approach could open positive prospects for scientific advance while honoring the diversity of opinions concerning our most fundamental moral principles. Such a solution is in keeping with the American spirit and would be a triumph for our Nation as a whole.

[The articles follow:]

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ALTERED NUCLEAR TRANSFER AS A MORALLY ACCEPTABLE MEANS FOR THE PROCUREMENT OF HUMAN EMBRYONIC STEM CELLS

(By William B. Hurlbut)

With the sequencing of the human genome and our increasing knowledge of the molecular mechanisms of basic cell functions, we are entering an era of rapid advance in the field of developmental biology. Current scientific interest in embryonic stem cells is a logical step in the progress of these studies and holds the hope of providing important research tools as well as possible therapeutic applications.

The ethical controversy surrounding cloning for biomedical research (CBR)[1] and human embryonic stem cell (ES cell) research arises from the fact that to obtain these cells living human embryos must be disaggregated and destroyed. Many Americans oppose such embryo destruction, believing that there is an implicit dignity and inviolability in the individual continuity of a human life from fertilization to natural death. Many others, however, believe that the benefits of advances in biomedical science outweigh these moral concerns.

[1] Also termed therapeutic cloning, somatic cell nuclear transfer, or nuclear transfer for the procurement of ES cells. For the difficulty of terminology, see President's Council 2002, chap. 3.

The present conflict over the moral status of the human embryo reflects deep differences in our basic convictions and is unlikely to be resolved through deliberation or debate. Likewise, a purely political solution will leave our country bitterly divided, eroding the social support and sense of noble purpose that is essential for the public funding of biomedical science. These concerns are already encoded in the Dickey Amendment, which prohibits the use of federal funds for embryo-destructive research and is the legislative foundation of the President's executive order restricting funding to ES cell lines created before August 9, 2001 (President's Council 2004, chap. 2). While there are currently no federally legislated constraints on the use of private funds for this research, there is a consensus in the scientific community that without NIH support for newly created ES cell lines, progress in this important realm of research will be severely constrained.

In joining with fellow members of the President's Council on Bioethics in support of a moratorium on CBR in July 2002, I considered this recommendation not an admission of ambivalence on matters of policy, but a recognition of the difficulty of the moral issues involved and an affirmation of the need for further discussion and deliberation (President's Council 2002). Throughout our proceedings over the past three years, it has become increasingly apparent that without clear and distinct moral principles, grounded in scientific evidence and reasoned moral argument, no policy can be effectively formulated or enforced. Most specifically, the proposed limitation of 14 days for research on human embryos and the prohibition against implantation appear to be arbitrarily set and therefore vulnerable to transgression through the persuasive promise of further scientific benefit. Clearly, a more thorough and thoughtful consideration of the moral status of the human embryo is warranted. It is in the spirit of this continuing discussion that I offer the personal perspectives that follow.

As our science is changing, so is the nature of our moral dilemmas. Each advance forces us to think more deeply about what it means to be human. As the scientific focus on genomics moves on to proteomics and now to the early stages of the study of development, we are confronted with the challenge of understanding the moral meaning of human life in its dynamics of change, as both potential and process. Concerns about cloning are likely to be just the beginning of a series of difficult ethical issues related to embryo experimentation and medical intervention in developing life. In addition, advances in developmental biology will open more deeply the ethical dilemmas of human-animal hybridization, extra-corporeal gestation, and genetic and cellular enhancement. Driven by the vast range of research applications and opportunities for clinical interventions in disease and disability (especially the open-ended possibilities promised by regenerative medicine), this technology will be powerfully propelled into the forefront of medical science.

Given the complex course of science and the drive to its development, any moral assessment of CBR or human ES cell research must describe the central human goods it seeks to preserve, the range and boundaries of these values, and the broad implications for science and society. Such an assessment should serve the dual purpose of helping to define the moral dangers while clearing the course for the fullest and most open future for scientific investigation and application.

MORAL PRINCIPLES

Although there are already numerous promising approaches for research on human development even without cloning techniques, I believe this technology could provide valuable tools for scientific inquiry and medical advance. In my judgment, the moral imperative to foster an increase of knowledge and new modes of therapeutic intervention weighs heavily in the equation of consideration. Nonetheless, I believe that, as they stand, current proposals for CBR and human ES cell procurement will breach fundamental moral goods, erode social cohesion, and ultimately constrain the promise of advances in developmental biology and their medical applications. However, there may be morally acceptable ways to produce ES cells through nuclear transfer (the technique used for CBR) that could both preserve our commitment to our fundamental moral principles and strengthen our appreciation of the significance of developing life. Such a technique would sustain social consensus while opening positive prospects for scientific advance in ES cell research.

The principle of valuing human life as the fundamental good serves as the cornerstone of law for our civilization. In no circumstance is the intentional destruction of the life of an innocent individual deemed morally acceptable. Even where a right to abortion is given, for example, it is based on a woman's right not to be encumbered—a right of privacy, not a right to directly kill the fetus—and if the fetus is delivered alive during an abortion, there is a legal obligation to resuscitate and sustain its life. This valuing of human life is indeed the moral starting point for both

advocates and opponents of CBR. The principle of the inviolability of human life is the reciprocal respect that we naturally grant as we recognize in the other a being of moral equivalence to ourselves. Although different cultures and eras have affirmed this recognition in varied ways, I will argue that it is reasonable in light of our current scientific knowledge that we extend this principle to human life in its earliest developmental stages.

LIFE AS PROCESS

When looked at through the lens of science, it is evident that an individual human life cannot be described atemporally, but must be recognized in the full procession of continuity and change that is essential for its development. From conception, our unique genetic endowment organizes and guides the expression of our particular nature in its species and individual character. Fertilization initiates the complex integration and functional unity of a self-directing, developing organism that may live for a hundred years or more. In both character and conduct, the zygote and subsequent embryonic stages differ from any other cells or tissues of the body; they contain within themselves the organizing principle of the full human organism.

This is not an abstract or hypothetical potential in the sense of mere possibility, but rather a potency, an engaged and effective potential-in-process, an activated dynamic of development in the direction of human fullness of being. For this reason, a zygote (or a clonote) differs fundamentally from an unfertilized egg, a sperm cell, or later somatic cells: it possesses an inherent organismal unity and potency that such other cells lack. Unlike an assembly of parts in which a manufactured product is in no sense "present" until there is a completed construction, a living being has a continuous unfolding existence that is inseparable from its emerging form. The form is itself a dynamic process rather than a static structure. In biology, the whole (as the unified organismal principle of growth) precedes and produces the parts. It is this implicit whole, with its inherent potency, that endows the embryo with its human character and therefore its inviolable moral status. To interfere in its development is to transgress upon a life in process. The argument is sometimes made that potential should not be part of the moral equation, because of the low probability of successful development of the early embryo.[2] This, however, is itself an argument based on potential, in this case the lack of potential to develop normally. The fact that life in its early stages is extremely fragile and often fails is not an argument to lessen the moral standing of the embryo. Vulnerability does not render a life less valuable.

ACCRUED MORAL STATUS

The major alternative to the view that an embryo has an inherent moral status is the assertion that moral status is an accrued or accumulated quality related to some dimension of form or function. Several arguments have been put forward for this position.

Gastrulation

One such accrual argument is based on the idea that before gastrulation (designated as the 14th day), the embryo is an inchoate clump of cells with no actuated drive in the direction of distinct development.[3] It is argued that the undifferentiated

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[2] The argument based on probability fails because it does not acknowledge the continuity of essential nature that characterizes an organism across its various stages of development. Such an argument might hold some weight if one could argue that a given stage of development represents an emergent state in which a newly manifest property is in ontological discontinuity with the material from which it emerged. At first consideration, this seems true of all biological systems where the whole reveals properties unpredicted within the parts. The problem in this line of reasoning, however, is that these properties are exactly that to which the whole is ordered, and so are inherent powers, "actual" within the whole when seen across time. To know what a biological being is, we must observe it over time, understand it across its life span. It is the essence of life that it is ordered to employ these leaps to emergent states as an agency in development. New realities will emerge; this is established in the potency of the developing organism.

[3] The differentiation of the trophoblast, which is evident by day four, is sometimes considered as distinct from the embryo itself. However, in light of current scientific evidence, it should be recognized as an inextricable component of the embryo, involved in a multitude of dynamic interactions essential for embryogenesis. The fact that it participates in the formation of the extra-embryonic membranes that are left behind at birth does not make it less central to the embryonic being and its development. Throughout the continuum of human life, cells, tissues, and organs are reabsorbed, transcended, and transformed: examples include the umbilical vein and arteries (which become supporting ligaments), neural cells (more than half of which are

Continued

quality of the blastocyst justifies its disaggregation for the procurement of stem cells, while the evident organization at gastrulation reveals an organismal integrity that endows inviolable moral status to all subsequent stages of embryological development. Scientific evidence, however, supports the argument that from conception there is an unbroken continuity in the differentiation and organization of the emerging individual life. The anterior-posterior axis appears to be already specified within the zygote, and early cell divisions (at least after the eight-cell stage) exhibit differential gene expression and unequal cytoplasmic concentrations of cell constituents, suggesting distinct cellular fates (Gardner 2001; Grabel et al. 1998; Piotrowska and Zernicka-Goetz 2001).This implies that the changes at gastrulation do not represent a discontinuity of ontological significance, but merely the visibly evident culmination of more subtle developmental processes (at the cellular level) driving in the direction of organismal maturity.

Twinning

Another argument for accrued moral status is that as long as an embryo is capable of giving rise to a twin, it cannot be considered to have the moral standing of an individual. There is the obvious objection that as one locus of moral status becomes two, it does not diminish but increases the moral moment. But perhaps more substantially, this argument actually supports the notion that crucial dimensions of individuation (and their disruption that results in twinning) are already at work in the blastocyst, the stage at which most twinning occurs. Monozygotic twinning (a mere 0.4 percent of births) does not appear to be either an intrinsic drive or a random process within embryogenesis. Rather, it is a disruption of normal development by a mechanical or biochemical disturbance of fragile cell relationships that provokes a compensatory repair, but with the restitution of integrity within two distinct trajectories of embryological development (da Costa et al. 2001).[4] In considering the implications of twinning for individuation, one might ask the question from the opposite perspective. What keeps each of these totipotent cells from becoming a full embryo? Clearly, crucial relational dynamics of position and intercellular communication are already at work establishing the unified pattern of the emerging individual (Wang et al. 2004). From this perspective, twinning is not evidence of the absence of an individual, but of an extraordinary power of compensatory repair that reflects more fully the potency of the individual drive to fullness of form.

Implantation

Some have argued that the implantation of the embryo within the uterine lining of the mother constitutes a moment of altered moral status. Implantation, however, is actually a process that extends from around the sixth or seventh day to about the 11th or 12th day, when the uteroplacental circulation is established. This complex circulatory exchange extends the earlier relationship between mother and embryo in which physiological conditions, including the diffusion of essential nutrients and growth factors, sustained the life and nourished the development of the pre-implantation embryo. Although these early conditions can be artificially simulated, as with in vitro fertilization (IVF), the delicate balance of essential factors and their effect on development is evidence of the crucial contribution of the mother even in the first week of embryogenesis (Fernández-Gonzalez et al. 2004). Changes in the intricate interrelations between mother and infant cannot be viewed as an alteration of moral status, but as part of the ongoing epigenetic process all along the continuum of natural development that begins with conception and continues into infancy. This continuity implies no meaningful moral marker at implantation.

Function

Arguments for a change in moral status based on function are at once the most difficult to refute and to defend. The first and most obvious problem is that the essential functions (even their minimal criteria and age of onset) are diverse and arbitrarily assigned. Generally they relate to the onset of sentience, awareness of pain, or some apparently unique human cognitive capability such as consciousness. But

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culled by apoptosis), and immune organs such as the thymus (which shrivels in an adult). We do not just develop and then age, but undergo a continuous transformation and fuller manifestation of our organismal nature present within the earliest embryo.

[4] The fact that these early cells retain the ability to form a second embryo is testimony to the resiliency of self-regulation and compensation within early life, not the lack of individuation of the first embryo from which the second can be considered to have "budded off." Evidence for this may be seen in the increased incidence of monozygotic twinning associated with IVF by blastocyst transfer. When IVF embryos are transferred to the uterus for implantation at the blastocyst stage, there is a two- to ten-fold increase in the rate of monozygotic twinning, apparently due to disruption of normal organismal integrity.

if human moral worth is based on actual manifest functions, then does more of a particular function give an individual life a higher moral value? And what are we to make of the parallel capacities in animals that we routinely sacrifice for food and medical research? Furthermore, what becomes of human moral status with the degeneration or disappearance of such a function? While we might argue that our relational obligations change along with changes in function, such as those that occur with senile dementia, we would not sanction a utilitarian calculus and the purely instrumental use of such persons no matter how promising the medical benefits might be. The diagnostic requirements of "brain death" for removing organs for transplantation, far from being a justification for interrupting a developing life before "brain birth," actually point to the moral significance of potential and the stringency of the criteria for irreversible disintegration and death.

From a scientific perspective, there is no meaningful moment when one can definitively designate the biological origins of a human characteristic such as consciousness. Even designations such as "the nervous system" are conceptual tools, reifications of the parts of what is actually an indivisible organismal unity. Zygote, morula, embryo, fetus, child, and adult: these are conceptual constructions for convenience of description, not distinct ontological categories. With respect to fundamental moral status, therefore, as distinguished from developing relational obligations, the human being is an embodied being whose intrinsic dignity is inseparable from its full procession of life and always present in its varied stages of emergence.

A BRIGHT LINE AT CONCEPTION

If the embryo has an inherent moral status that is not an accrued or accumulated quality related to some dimension of form or function, then that moral status must begin with the zygote (or clonote). Anything short of affirming the inviolability of life across all of its stages from zygote to natural death leads to an instrumental view of human life. Such a revocation of our most fundamental moral principle would reverse a long and overarching trend of progress in moral awareness and practice in our civilization. From human sacrifice, to slavery, child labor, women's rights, and civil rights, we have progressively discerned and prohibited practices that subject the individual to the injustice of exploitation by others. The reversal of such a basic moral valuation will extend itself in a logic of justification that has ominous implications for our attitude and approach to human existence. This is not a mere "slippery slope," where we are slowly led downward by the ever more desirable extension of exceptions to moral principle. It is, rather, a "crumbly cliff," where the very utility of abrogating a basic moral prohibition carries such convenience of consequence that the subsequent descent is simply practice catching up with principle.

The inviolability of human life is the essential foundation on which all other principles of justice are built, and erosion of this foundation destabilizes the social cooperation that makes possible the benefits of organized society. Medicine is especially vulnerable to such effects, since it operates at the intrinsically moral interface between scientific technique and the most tender and sensitive dimensions of personal reality in the vulnerable patient. As we descend into an instrumental use of human life, we destroy the very reason for which we were undertaking our new therapies; we degrade the humanity we are trying to heal.

The promise of stem cells lies beyond simple cell cultures and cell replacement therapies. The 14-day marker will not hold up to logical argument.[5] The technological goal is to produce more advanced tissues, organs, and possibly even limb primordia. Producing such tissues may require the complex cell interactions and microenvironments now available only through natural gestation. Embryonic development proceeds within the context of a highly refined spatial and temporal niche of organized complexity of positional cues, signal diffusion, and cell-cell contact between cellular lineages of diverse types (Nishimura et al. 2002).The benefits of implanting cloned embryos (either into the natural womb or possibly an artificial endometrium) so as to employ the developmental dynamics of natural embryogenesis

[5] The designation of 14 days as the moral boundary for embryo experimentation is in the category of a "received tradition," almost a superstition in the sense that it is a belief in a change of state without a discernible cause.The validity of this designated moral marker has not been reexamined in the light of recent advances in our understanding of developmental biology. As a moral marker of ontological change, 14 days makes no sense. Even if one disagrees with the discussion above, the date should be set earlier: implantation is complete by the 12th day, the onset of gastrulation occurs as the primitive streak between the 12th and 14th days, and twinning is rare after the ninth day. Furthermore, it is worth noting that 14 days is not of current scientific relevance, since stem cells can be procured at the four- to five-day stage and, with present technology, human embryos can sustain viability in culture for only eight to nine days.

seem self-evident. The implantation of cloned embryos for the production of patient-specific tissue types to bypass problems of immune rejection would further extend the logic of the instrumental use of developing life. The public pressure that has already been brought to bear on the politics of stem cells and cloning by patient advocacy groups has provoked such a sense of promise that it may propel the argument for allowing implantation of cloned embryos. Different people may have different limits to the duration of gestation they find morally acceptable, but in light of the current sanction of abortion up to and beyond the end of the second trimester, it is difficult to argue that creation, gestation, and sacrifice of a clone to save an existing life is a large leap in the logic of justification.

ALTERED NUCLEAR TRANSFER

While maintaining a bright line at conception safeguards our most fundamental moral principle, the challenge remains to find an acceptable method of drawing on the great medical promise of CBR and ES cells while precluding their use in ways that degrade the dignity of human existence. Some proponents of CBR maintain that the laboratory creation of the cloned embryo makes it a "pseudoembryo" or "artifact," a product of human technological production.They point to the unnatural means of its creation and the low probability of successful development to birth evident in most animal studies. Although we have no experience with the gestation of cloned human embryos (and only a single study involving gestation of nonhuman cloned primates), one significant difference from natural fertilization is that animal cloning consistently produces a high percentage of defective offspring (Jaenisch 2004). Indeed, most of the products of cloning never make it past early developmental stages, and among those that do, many die during gestation. Some argue that this high rate of early failure of development means that all products of nuclear transfer should be considered as lacking the moral standing of a natural embryo. The problem with this assertion is that, at least in some cases, the cloned embryo appears to share the developmental potential of the product of natural fertilization.

Why some of the products of nuclear transfer proceed to develop while others do not is an important scientific question. The answer to this question is relevant to the search for a morally acceptable method for the procurement of ES cells and the proposal that follows. Evident abnormality during early development does not, of itself, preclude the formation of a whole and healthy offspring. IVF embryos often exhibit slower division rates and fewer cells at the equivalent stages of naturally conceived embryos (Barry Behr, Stanford University, personal communication). Likewise, at least in mice, intracytoplasmic sperm injection appears to disrupt the natural specification of cell fates and body axes normally associated with the point of sperm entry. In these cases, the capacity for regulation, for robust repair and restitution of the normal pattern of development, is evidence of the organizational integrity and unified principle of growth that characterizes a genuine organism. This capacity, together with the more fundamental powers of self-development and self-maintenance, is a crucial determinant in the moral status of any product of fertilization or nuclear transfer. To be rightly designated a human embryo with moral standing, an entity must have the organismal character of a living being.[6] Clearly, many products of nuclear transfer lack these fundamental capacities of organisms, but since some are capable of integrated development, the fact of cloning alone does not establish a different moral status for the entity produced. Could we, however, use our advancing knowledge of developmental biology to create an entity that consistently lacks the qualities and capabilities essential to be designated a human embryonic organism? By intentional alteration of the somatic cell nuclear components or the cytoplasm of the oocyte into which the nucleus is transferred, could we truly create an artifact (a human creation for human ends) that is biologically and morally more akin to a tissue or cell culture?

There are several possible approaches that might allow the production of ES cells without the creation and destruction of a human embryo. The ideal solution, one that many scientists believe will eventually be possible, would be the direct reprogramming of adult cells to become the functional equivalents of ES cells. In nat-

[6] The word organism implies organization, an overarching principle of unity, a cooperative interaction of interdependent parts subordinated to the good of the whole. As a living being, an organism is an integrated, self-developing, and self-maintaining unity under the governance of an immanent plan. The philosopher Robert Joyce (1978) explains: "Living beings come into existence all at once and then gradually unfold to themselves and to the world what they already but only incipiently are." To be a human organism is to be a whole living member of the species Homo sapiens, to have a human present and a human future evident in the intrinsic potential for the manifestation of the species typical form. Joyce continues: "No living being can become anything other than what it already essentially is."

ural embryogenesis, ES cells are produced within a restricted area (the inner cell mass) of a blastocyst.[7] Over the first few days of development, a series of cell signals induces the specific pattern of gene expression that characterizes ES cells and gives them their pluripotency, their capacity to subsequently produce all the cell types of the human body. With an understanding of the exact molecular nature of these signals, it may be possible to bypass embryogenesis and directly induce this transformation in adult cells. For example, as suggested by Alan Trounson of Monash University, Australia, we may be able to reprogram the nucleus of a somatic cell by transplanting it into the cytoplasm of an existing ES cell (personal communication). Unfortunately, it may be many years before our scientific knowledge and control of these factors will make this approach feasible.

More immediately, there may be ways to obtain ES cells by harnessing partial organic trajectories apart from the full natural system of embryonic development. Using the techniques of nuclear transfer, but with the intentional alteration of the nucleus before transfer, we could construct a biological entity that, by design and from its very beginning, lacks the attributes and capacities of a human embryo. Studies with mice already provide evidence that such a project of altered nuclear transfer (ANT) may be able to generate functional ES cells from a cellular system that lacks the intrinsic potential of an actual organism, but possesses the limited organic powers of a tissue or cell culture. This proposal shifts the ethical debate from the question of when a normal embryo is a human being with moral worth, to the more fundamental question of what component parts and organized structure constitute the minimal criteria for considering an entity a human organism.[8]

For practical implementation of ANT, a working definition of the term "human embryonic organism" might be any entity, regardless of its source or means of production, which, when provided the support and nurture of a natural gestational environment (or its technological equivalent), has the intrinsic potential to express the minimal manifestations of form and function that characterize a human organism. This still leaves open the discussion of the exact definition of such minimal developmental potentiality, but affirms that the moral status of such an entity is related to its intrinsic nature, not its mode of creation or present location. It is important to recognize, however, that such criteria of minimal developmental potentiality are only of secondary concern for ANT, where the most practical and (morally uncontroversial) technique may involve an alteration at a far more fundamental level. For a discussion of the defining criteria of a human organism, see Ashley 2001; Grisez 1989; Huarte and Suarez 2004.

FAILURES OF FERTILIZATION AND PARTIAL DEVELOPMENT

The activation of an egg by the penetration of a sperm (or the equivalent events in nuclear transfer/cloning) triggers the transition to active organismal existence, with its potential for development toward the adult human form. But without all of the essential elements (the necessary complement of chromosomes, proper chromatin configuration, the cytoplasmic factors for gene expression, etc.), there can be no living whole, no organism, and no human embryo. Recent scientific evidence suggests that incomplete combinations of the necessary elements—"failures of fertilization"—are the fate of many, perhaps most, early natural initiations in reproduction. ANT proposes the artificial construction of a cellular system mimicking these natural examples, one that lacks the essential elements for embryological development but contains a partial developmental potential capable of generating ES cells.

Many naturally occurring failures of fertilization may still proceed along partial trajectories of organic growth without being true organisms. For example, grossly abnormal karyotypes, such as trisomies of chromosome 1, will form a blastocyst but will not implant (Boué, Boué, and Gropp 1985). Even an enucleated oocyte, when artificially activated, has the developmental momentum to divide to the eight-cell stage, but clearly is not an organism. The mRNA for the protein synthesis that drives these early cell divisions is generated during the maturation of the egg and then activated after fertilization. Like a spinning top, the cells contain a certain bio-

[7] It is important to note that ES cells may be a product of laboratory isolation and culture and may exhibit properties quite different from their natural counterparts within the developing embryo.

[8] The mouse study by Chawengsaksophak and Rossant (2004) did not involve ANT, but it did demonstrate that ES cells may be procured where a gene essential at a fundamental level of embryogenesis is knocked out. As discussed below, whether an entity with such a dramatic disruption of development should be characterized as a "disabled" embryo or as a non-embryonic entity is an important consideration. Nonetheless, ANT could involve an intervention or complementary interventions at an even earlier and more fundamental level. Defining the moral boundary will be a crucial step in the implementation of this project.

logical momentum that propels a partial trajectory of development, but unlike a normal embryo they are unable to bootstrap themselves into becoming an integrated and self-regulating organismal entity.

Some of these aberrant products of fertilization that lack the qualities and characteristics of an organism appear to be capable of generating ES cells or their functional equivalent (Byrne, Simonsson, and Gurdon 2002). Mature teratomas are neoplasms that generate all three primary embryonic germ cell types, as well as more advanced cells and tissues, including partial limb and organ primordia. Yet these chaotic, disorganized, and nonfunctional masses entirely lack the structural and dynamic character of organisms. Teratomas may occur as benign ovarian tumors that are, at least in some cases, derived by spontaneous and disorganized development of activated eggs. They generally have a complete karyotype (46XX), and they produce a diversity of cell and tissue types that suggests that they may proceed through a developmental process similar enough to natural embryogenesis to produce pluripotent stem cells. In fact, through intentional parthenogenetic activation of monkey eggs (which mimics teratoma formation), Vrana et al. (2003) were able to coax them to a blastocyst-like stage and harvest ES cells. Serious scholars and scientists, including the geneticist and Dominican priest Nicanor Austriaco (2002), have made moral arguments supporting such a source of human ES cells. Furthermore, there are already patent applications for such a procedure.

The disorganized character of teratomas appears to arise not from changes in the DNA sequence, but from genetic imprinting, an epigenetic modification that affects gene expression. In natural reproduction the sperm and egg have different, but complementary, patterns of imprinting, allowing a coordinated control of embryological development. When an egg is activated without a sperm, the trophectoderm and its lineages fail to develop properly. The differentiation of the trophectoderm and the inner cell mass (which forms the ES cells) is considered the first globally coordinated divergence into distinct cell lineages. The trophectoderm is necessary for the cross-inductions that are the foundation for all further coordinated and organized growth of the embryo. Later it contributes to the formation of the extra-embryonic membranes, but earlier in development it is crucial for both embryo structural integrity and the development of a normal inner cell mass. In the absence of the complementary genetic contribution of the male, the activated egg is simply inadequately constituted to direct the integrated development characteristic of human embryogenetic process.

Interestingly, an inverse failure of formation characterizes development driven only by genetic elements from the male, where the complementary contribution of the female is missing. In complete hydatidiform moles an egg missing its nucleus is fertilized by one or more sperm. This time, lacking the maternal genetic contribution with its complementary imprinted genes, there is an overgrowth of trophectoderm with no apparent ES-like cells and little or nothing in the way of fetal parts.

Recent evidence suggests that in their development both of these disorganized growths may proceed to the blastocyst stage. They may appear on visual inspection to be growing normally, but they carry an intrinsic insufficiency at the molecular level that renders them incapable of forming the body axes and essential infrastructure characteristic of human embryogenesis. (Clearly, the method and level of analysis we use will influence our interpretation of the identity and moral valuation of a thing. This highlights the importance of evaluating products of fertilization and nuclear transfer not simply by visual observation but also against the molecular signature that characterizes natural embryos.)

The exact cause of the aberrant and disordered growth of these "failures of formation" is not fully understood, but studies with parthenogenetic mice provide a remarkable window into the organizing (or disorganizing) role of a single genetic alteration. Using a technique similar to ANT, Japanese scientists produced a fully formed mouse by combining chromosomes from two oocytes, but with a single modification of an imprinted region to simulate the necessary male contribution (Kono et al. 2004). With this one change in genetic regulation directly affecting expression of just two genes, instead of disordered growth, normal offspring were produced. This simple restoration of the male/female complementarity of gene expression resulted in changes in the downstream gene expression of over a thousand other genes.

SYNTHETIC AND SYSTEMS BIOLOGY

This striking example of our increasing power to intervene and alter natural processes points to a coming era of challenging ethical dilemmas through advances in developmental biology. With new tools from cytology to synthetic biology, we are

gaining control not just of component parts and their partial trajectories of growth, but of the principles and dynamics of organismal systems. Beyond highlighting our increasing powers over developmental biology, the parthenogenetic mouse points to another level of advance in our understanding: our new appreciation of systems biology, in which we see how even an alteration in a single gene can affect the entire balance of an enormous network of biochemical processes within the cell.

Systems biology offers us a renewed appreciation of an organism as a living whole, a dynamic network of interdependent and integrated parts. There are essential subsystems of growth (cells, tissues, and organs), but a living being is more than the sum of its parts, and the parts are dependent on the integrated unity of the whole. Fully constituted, an organism is a self-sustaining, unified being with an inherent principle of organization that orders and guides its continuity of growth. In the human embryo, this principle of organismal unity is an activated dynamic of development in the direction of the mature human form. If severed from the whole, partial subsystems may temporarily proceed forward in development, but without the environment of their organismal system, they will ultimately become merely disorganized cellular growth. ANT proposes that small but precisely selected alterations will allow the harnessing of partial developmental trajectories apart from their full natural context in order to produce ES cells.

CDX2

There are numerous potential approaches to such a project, involving the alteration of genes necessary for early intercellular signaling, cell differentiation, or integrated patterning of development. Of course, there must first be a thorough discussion to decide what level of alteration would be consistent with both the scientific and moral goals of this project. For the sake of discussion, one possibility might be the alteration of Cdx2, a gene essential for the differentiation of the trophectoderm (which, together with the formation of the inner cell mass, reveals the first globally coordinated segregation of cell lineages). This may not be an acceptable final solution, but examining it as a specific example could allow us to consider the necessary criteria for scientific success and moral accept-ability.[9] ANT must not be simply identified with Cdx2 alteration, however, for the general proposal encompasses a wide range of alternative procedures.

Janet Rossant and her colleagues have shown Cdx2 to be an essential component of early embryogenesis (Tam and Rossant 2003). The gene is expressed immediately after compaction (around the 16- to 32-cell stage) and is necessary for the differentiation of the trophectoderm, the outer layer of cells that seals the embryo and controls the flow of water and ions to the inner cavity (Felix Block, University of Leicester, personal communication). Although the trophectoderm cell lineage is crucial in the formation of the extra-embryonic membranes, it is properly considered part of the embryo, as it plays a central role in the interactive cellular inductions that generate all subsequent embryonic development. Studies confirm that a functional trophectoderm is essential in embryogenesis. In mice, when Cdx2 is not expressed there is only a partial and disorganized developmental process resulting in a visibly abnormal blastocyst. Nonetheless, there is the formation of an inner cell mass from which functional ES cells have been harvested (Chawengsaksophak et al. 2004). For the purposes of ANT, Cdx2 might be deleted from the somatic cell nucleus prior to transfer. Once the ES cells have been procured, the gene could be re-installed to restore a full genetic constitution. Alternatively, the same goal might be accomplished through temporary gene silencing using RNA interference. Indeed, some combination of alterations in gene expression could be affected by the complementary employment of several systems of genetic knock-out and/or knock-down.

This technologically created, limited cellular system, from which the ES cells would be obtained, would fail to establish even the most basic features of human organismal infrastructure and would be incapable of implantation. A deficiency at the first complementary differentiation of cell types—the formation of the

[9] The ideal candidate would be a gene essential for the earliest expressions of organismal integrity, such that the "partial trajectory of growth" would lack the coordinated development of natural embryogenesis but be more akin to an "inner cell mass culture." With the deficiency of a gene such as cdx2, which (by current evidence) is not expressed before the 16-cell stage, some might consider that the created entity is a "disordered" embryo. This is a serious concern and must be given careful consideration, but it is, of course, dependent on the definition of an embryo. It is possible, however, that this "deficiency" may be expressed earlier and at a more fundamental level of organization than that which produces a teratoma. While some might then argue that a teratoma is also a disordered embryo, a more convincing verdict would be that such an entity lacks the essential nature of a human embryonic organism and, as a pathological process, would be a proper target of therapeutic intervention at any stage in its development.

trophectoderm and the inner cell mass-means the absence of the most fundamental order. According to Dr. Maureen Condic, a developmental biologist at the University of Utah, "When [the] trophoblast does not form, subsequent development follows a chaotic pattern, suggesting that organismal development has not been 'disrupted' in the absence of [the] trophoblast, but rather that an organism never existed in the first place" (Condic and Condic, in press).

The resulting cells would have no inherent principle of unity, no coherent drive in the direction of the mature human form, and no claim on the moral status due to a developing human life. Rather, such a partial disorganized organic potential would more rightly be designated a "biological artifact"—a human creation for human ends. The fact that some part of such a constructed entity will carry a certain momentum of development is morally analogous to the fact that we can grow skin in a tissue culture and may one day grow whole organs or limbs in isolation. Lacking crucial elements in its fundamental constitution, such an entity would never rise to the level of a living being. When the overarching integration of essential parts and functions is not present (or, as in the "brain dead" organ donor, no longer present), there is no living organism and therefore there is no being with human moral status.

ADVANTAGES OF ALTERED NUCLEAR TRANSFER

Unlike other proposals for ethical procurement, ANT would allow a uniquely flexible approach by providing a wide range of ES cell types that would have the full normal complement of human chromosomes, could be of specific genetic types for tissue compatible transplantation, and would not carry the danger of zoonotic contamination.

In addition, this technique would offer a far wider range of scientific and medical possibilities than ES cell lines derived from "leftover" IVF embryos, including generation of diverse and pre-designed ES cell lineages for disease modeling and pharmaceutical development. Indeed, in allowing controlled and reproducible experiments, ANT might serve as a temporary bridge to transcendent technologies such as direct nuclear reprogramming. Furthermore, in establishing a morally acceptable means for the procurement of ES cells, this important realm of scientific investigation would be opened to federal funding and the advantages of both broad public support and cooperative research collaboration on a national level.

ANT could also unburden ES cell research from the additional ethical concerns of the "leftover" IVF embryos, including the attendant clinical and legal complexities in a realm of great personal and social sensitivity. The one remaining link with IVF, the procurement of oocytes, is a subject of intense scientific research, and there appear to be several prospects for obtaining eggs without the morally dubious and expensive superovulation of female patients. These include the use of eggs left unfertilized from IVF procedures (nearly half of all eggs produced, some of which will fertilize with intra-cytoplasmic sperm injection or nuclear transfer), xenotransplantation of human cadaveric ovaries or ovaries from oophorectomies transplanted into animals, in vitro maturation of ovarian tissue, and possible laboratory production of oocytes from ES cells.

ETHICAL HARNESSING OF PARTIAL DEVELOPMENTAL POTENTIAL

All cloning procedures where living embryos are produced should rightly be recognized as acts of reproduction, even if these nascent human lives are intended for disaggregation early in their development for projects of scientific research. The intention in creating an intrinsically limited "biological artifact" through ANT would not be one of reproduction and disaggregation, but simply the desire to draw on natural organic potential through technological manipulation of biological materials. This intention is in keeping with the purposes of scientific research and medical therapy in which many "unnatural" manipulations are used for human benefit.

The crucial principle of any approach employing ANT, however, must be the *preemptive* nature of the intervention. This process does not involve the creation of an embryo that is then altered to transform it into a non-embryonic entity. Rather, the proposed genetic alteration is accomplished *ab initio*: the entity is brought into existence with a genetic structure insufficient to generate a human embryo. From the beginning and at every point along its development, it cannot be designated a living being. No human embryo would be created, hence none would be violated, mutilated, or destroyed in the process of stem cell harvesting. If such a limited biological entity were accorded a certain cautionary respect (as with all human tissues), even though not the full protection of human life, this project would not compromise any fundamental moral principles. Moreover, such techniques could be developed using

animal models and confidently extended to work with human cells without engaging in research that involves the destruction of human embryos.

Over the course of the previous century, we have contended with ethical controversies over blood transfusion, tissue and organ transplantation, and the transfection of human genes into experimental animals. In this century we will be confronted by a series of even more challenging ethical questions related to the dynamic systems of developmental biology. Just as we have learned that neither genes, nor cells, nor even whole organs define the locus of human moral standing, in this era of developmental biology we will come to recognize that cells and tissues with "partial generative potential" may be used for medical benefit without a violation of human dignity.

CONCLUSION

The moral distinctions essential to discern and define the categories of organism, embryo, and human being will be vital as we go forward with scientific research involving human embryonic stem cells, chimeras, and laboratory studies of fertilization and early embryogenesis. Advances in developmental biology will depend on clarifying these categories and defining the moral boundaries in a way that at once defends human dignity while clearing the path for scientific progress.

At this early stage in our technological control of developing life, we have an opportunity to break the impasse over stem cell research and provide moral guidance for the biotechnology of the future. This may require a constructive refinement of some aspects of moral philosophy, together with creative exploration of scientific possibilities, but any postponement of this process will only deepen the dilemma as we proceed into realms of technological advance unguided by forethought. We must initiate the cooperative dialogue that is essential to frame the moral principles that can at once defend human dignity and promote the fullest prospects for scientific progress and its medical applications.

REFERENCES

Ashley, B. 2001. Cloning, Aquinas, and the embryonic person. *Natl Catholic Bioethics Q* 1:189–202.

Austriaco, N.P. 2002. On static eggs and dynamic embryos: A systems perspective. *Natl Catholic Bioethics Q* 2:659–83.

Boué, A., J. Boué, and A. Gropp. 1985. Cytogenetics of pregnancy wastage. *Adv Hum Genet* 14:1–57.

Byrne, J.A., S. Simonsson, and J.B. Gurdon. 2002. From intestine to muscle: Nuclear reprogramming through defective cloned embryos. *Proc Natl Acad Sci USA* 99:6059–63.

Chawengsaksophak, K., et al. 2004. Cdx2 is essential for axial elongation in mouse development. *Proc Natl Acad Sci USA* 101:7641–45.

Condic, M.L., and S.B. Condic. n.d. Defining organisms by organization. Forthcoming. da Costa, A.L.E., et al. 2001. Monozygotic twins and transfer at the blastocyst stage after ICSI. *Human Reprod* 16:333–36.

Fernández-Gonzalez, R., et al. 2004. Long-term effect of in vitro culture of mouse embryos with serum on mRNA expression of imprinting genes, development, and behavior. *Proc Natl Acad Sci USA* 101:5880–85.

Gardner, R.L. 2001. Specification of embryonic axes begins before cleavage in normal mouse development. *Development* 128:839–47.

Grabel, L., et al. 1998. Using EC and ES cell culture to study early development: Recent observations on Indian hedgehog and BMPs. *Int J Dev Bio*l 42:917–25.

Grisez, G. 1989. When do people begin? *Proc Am Catholic Philosophical Assn* 63:27–47.

Huarte, J., and A. Suarez. 2004. On the status of parthenotes: Defining the developmental potentiality of a human embryo. *Natl Catholic Bioethics Q* 4:755–70.

Jaenisch, R. 2004. Human cloning: The science and ethics of nuclear transplantation. *N Engl J Med* 351:2787–91.

Joyce, R.E. 1978. Personhood and the conception event. *New Scholasticism* 52:97–109.

Kono, T., et al. 2004. Birth of parthenogenetic mice that can develop into adulthood. *Nature* 428:860–64.

Nishimura, E.K., et al. 2002. Dominant role of the niche in melanocyte stem-cell fate determination. *Nature* 416:854–60.

Piotrowska, K., and M. Zernicka-Goetz. 2001. Role of sperm in spatial patterning of the early mouse embryo. *Nature* 409:517–21.

President's Council on Bioethics. 2002. *Human cloning and human dignity: An ethical inquiry.* Washington, DC: President's Council on Bioethics. Repr. New York: Public Affairs, 2002. http://www.bioethics.gov/reports/cloningreport/index.html.
President's Council on Bioethics. 2004. *Monitoring stem cell research.* Washington, DC: President's Council on Bioethics. http://www.bioethics.gov/reports/stemcell/index. html.
Tam, P.P., and J. Rossant. 2003. Mouse embryo chimeras: Tools for studying mammalian development. *Development* 130:6155–63.
Vrana, K.E., et al. 2003. Nonhuman primate parthenogenetic stem cells. *Proc Natl Acad Sci USA* 100 (suppl. 1):11911–16.
Wang, Q.T., et al. 2004. A genome-wide study of gene activity reveals developmental signaling pathways in the preimplantation mouse embryo. *Dev Cell* 6:133–44.

[The President's Council on Bioethics]

ALTERED NUCLEAR TRANSFER AS A MORALLY ACCEPTABLE MEANS FOR THE PROCUREMENT OF HUMAN EMBRYONIC STEM CELLS

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INTRODUCTION

I want to present some ideas that seem worthy of discussion and possibly preliminary scientific investigation. Those of us who have been working on these ideas have already explored some of the philosophical and technical dimensions, but there are important theoretical and practical issues that need further consideration.

We offer these ideas not as an assertion of certitude, but as a promising avenue of inquiry, one that might move us beyond our current conflict over the procurement of ES cells by providing a "third option," a technological solution to our moral impasse.

In the broadest sense we propose a creative exploration of a full range of scientific approaches. More specifically, we raise the possibility that, using the technique of Nuclear Transfer, it may be possible to produce ES cells within a limited cellular system that is biologically and morally akin to a complex tissue culture, and thereby bypass moral concerns about the creation and destruction of human embryos.

I want to make two points very clear from the beginning. What is proposed here is a concept, an approach to a problem; the specific examples, which may or may not be morally acceptable or scientifically feasible, are offered only to make clear the larger concept, and as a starting point for discussion.

Second, we are at the stage of a constructive dialogue; if these ideas are deemed feasible, extensive studies with animal models must follow. We do not propose any projects involving human cells until we can be certain that embryos are not created by these methods.

POLITICAL IMPASSE AND COMPETING GOODS

The present conflict over the moral status of the human embryo reflects deep differences in our basic convictions and is unlikely to be resolved through deliberation or debate. Many Americans oppose embryo destruction for the procurement of stem cells, believing that there is an implicit dignity and inviolability in the individual continuity of a human life from fertilization to natural death. Many others, however, believe that the benefits of advances in biomedical science outweigh these moral concerns.

A purely political solution will leave our country bitterly divided, eroding the social support and sense of noble purpose that is essential for the public funding of biomedical science. While there are currently no federally legislated constraints on the use of private funds for this research, there is a consensus opinion in the scientific community that without NIH support for newly created ESC lines, progress in this important realm of research will be severely constrained.

Notwithstanding this apparently irresolvable impasse, we believe there may be morally uncontroversial ways to obtain embryonic stem cells. Drawing on our increasing understanding and control of developmental biology, the technique of Altered Nuclear Transfer may allow us to generate ES cells even apart from the organismal system that is their natural origin.

LIFE AT CONCEPTION

In order to evaluate potential solutions and allow forward progress within moral consensus, we will have to understand the perspectives (and address the concerns) of those who believe that life begins at conception.

By this view, the most fundamental principle, on which all other moral principles are built, is the intrinsic dignity and inviolability of human life across all of its stages. In both constitution and conduct the zygote and all subsequent embryonic stages differ from any other cells or tissues of the body; they contain within themselves the organizing principle for the self-development and self-maintenance of the full human organism.

The activation of an egg by the penetration of a sperm, or the equivalent event in nuclear transfer/cloning, triggers the transition to active organismal existence, with the potential to develop into an adult human. But without all of the essential elements—the necessary complement of chromosomes, proper chromatin configuration, the cytoplasmic factors for gene expression, etc.—there can be no living whole, no organism, and no human embryo. Recent scientific evidence suggests incomplete combinations of the necessary elements—failures of fertilization—are the fate of many, perhaps most, early natural initiations in reproduction. Altered nuclear transfer proposes the artificial construction of a cellular system mimicking these natural examples, a system that lacks the essential elements for embryological development but contains a partial developmental potential capable of generating embryonic stem cells.

FAILURES OF FERTILIZATION

It is important to realize that many of these naturally occurring failures of fertilization may still proceed along partial trajectories of organic growth without being actual organisms. For example, grossly abnormal karyotypes such as trisomies of chromosome number one (the largest chromosome, with the most genes) will form a blastocyst but will not implant.

Even an egg without a nucleus, when artificially activated, has the developmental power to divide to the eight-cell stage, yet clearly is not an embryo—or even an organism. The mRNA for the protein synthesis that drives these early cell divisions is generated during the maturation of the egg and then activated after fertilization. Like a spinning top, the cells contain a certain biological momentum that propels a partial trajectory of development, but unlike a normal embryo they are unable to bootstrap themselves into becoming an integrated and self-regulating organismal entity.

Some of these aberrant products of fertilization, which lack the qualities and characteristics of an organism, appear to be capable of generating ES cells or their functional equivalent. Mature teratomas are neoplasms that generate all three primary embryonic germ cell types as well as more advanced cells and tissues, including partial limb and organ primordial—and sometimes hair, fingernails and even fully formed teeth. Yet these chaotic, disorganized, and nonfunctional masses lack entirely the structural and dynamic character of organisms.

These benign ovarian tumors, are, in some cases, derived by spontaneous and disorganized development of activated eggs. They generally have a complete karyotype (46XX) and they produce a diversity of cell and tissue types that suggests that they may proceed through a developmental process similar enough to natural embryogenesis to produce pluripotent stem cells. In fact, through intentional parthenogenetic activation of monkey eggs (which mimics teratoma formation), one private U.S. company was able to coax them to a blastocyst-like stage and harvest ES cells. Serious scholars and scientists, including the geneticist and Dominican Priest Nicanor Austriaco, have made moral arguments supporting such a source of human ES cells. Furthermore, there may soon be patent applications for such a procedure.

The disorganized character of teratomas appears to arise not from changes in the DNA sequence, but from genetic imprinting, an epigenetic modification that affects gene expression (keeping some genes turned off and others on). In natural reproduction the sperm and egg have different, but complementary, patterns of imprinting, allowing a coordinated control of embryological development. When an egg is activated without a sperm, the trophectoderm and its lineages fail to develop properly. The differentiation of the trophectoderm and the inner cell mass (which forms the ES cells) is considered the first globally coordinated divergence into distinct cell lines. The trophectoderm is necessary for the cross inductions that are the foundation for all further coordinated and organized growth of the embryo. Later it contributes to the formation of the extra-embryonic membranes, but early in development it is crucial for both embryonic structural integrity and the development of a normal inner cell mass.

In the absence of the complementary genetic contribution of the male, the activated egg is simply inadequately constituted to direct the integrated development characteristic of human embryogenetic process.

Interestingly, an inverse failure of formation characterizes development driven only by genetic elements from the male, where the complementary contribution of the female is missing. In hydatidiform moles, an egg missing its nucleus is fertilized by one or more sperm. This time, lacking the maternal genetic contribution with its complementary imprinted genes, there is an overgrowth of trophectoderm with no apparent inner cell mass or ES-like cells, and little or nothing in the way of fetal parts.

Recent evidence suggests that in their development both of these disorganized growths may proceed to the blastocyst stage: they may appear on visual inspection to be growing normally, but they carry an intrinsic insufficiency making them incapable of the essential formation of body axes and infrastructure characteristic of human embryogenesis.

The cause of the aberrant and disordered growth of these "failures of formation" is not fully understood, but studies with parthenogenetic mice provide a remarkable window into the organizing (or disorganizing) role of a single genetic alteration. Employing a form of Altered Nuclear Transfer, Japanese scientists produced a fully formed mouse using only female chromosomes, but with a single modification of an imprinted region to simulate the necessary male contribution. With this one change in genetic regulation directly affecting expression of just two genes, instead of disordered growth, normal offspring were produced. To everyone's amazement, this simple restoration of the male/female complementarity of gene expression resulted in changes in the downstream gene expression of over a thousand other genes.

SYNTHETIC AND SYSTEMIC BIOLOGY

This striking example of our increasing power to intervene and alter natural processes points to a coming era of challenging ethical dilemmas through advances in developmental biology. With new tools from cytology to synthetic biology, we are gaining control of not just component parts and their partial trajectories of growth, but the very principles and dynamics of organismal systems.

Beyond highlighting our strange and challenging new powers over developmental biology, the parthenogenetic mouse points to another level of advance in our understanding: our new appreciation of systems biology, in which we see how even a small change of one gene can affect the entire balance of an enormous network of biochemical processes within the cell.

Systems biology offers us the view of an organism as a living whole, a dynamic network of interdependent and integrated parts. If severed from the whole, these partial subsystems may temporarily proceed forward in development, but without the larger environment of their organismal system, they will become merely disorganized cellular growth. ANT proposes that small (but precisely selected) genetic alterations will allow us to harness these subsystems of partial development, apart from their full natural organismal context, in order to produce ES cells.

ALTERED NUCLEAR TRANSFER

Eventually we may understand the biochemical factors that can transform a somatic cell to a pluripotent state. But while the ultimate goal for the generation of ES cells is the direct nuclear reprogramming of an adult nucleus, it may be many years before our scientific knowledge and control of cellular factors will make this approach feasible. More immediately, we may be able to use the techniques of Nuclear Transfer, but with the intentional alteration of the nucleus *before* transfer, to construct a biological entity that, by design and from its very beginning, lacks the attributes and capacities of a human embryo. Studies with mice already provide evidence this *Altered* Nuclear Transfer may be able to generate functional ES cells from a system that is not an embryo, but possesses the limited organic potential of a tissue or cell culture.

Cdx2

For the sake of specifics in this discussion, let me propose one particular example of how this could be accomplished. This may not be an acceptable ultimate solution, but it will allow us to consider the necessary criteria for scientific success and moral acceptability.

As well demonstrated in the work of Dr. Janet Rossant at Mt. Sinai Hospital in Canada, the gene *Cdx2* is essential for embryogenesis. This gene is expressed immediately after compaction (around the 16–32 cell stage), and is crucial for the dif-

ferentiation of the trophectoderm, the outer layer of cells that seals the embryo and controls the flow of water and ions to the inner cavity.

Although the trophectoderm cell lineage is the source of the extraembryonic membranes, it is properly considered an integral part of the embryo, as it plays a central part in the interactive cellular inductions that generate all subsequent embryonic development. Studies confirm that a functional trophectoderm is absolutely essential in embryogenesis. In experiments with mouse models, when *Cdx2* is not expressed there is only a partial and disorganized developmental process resulting in a visibly abnormal blastocyst. Nonetheless, there is the formation of an inner cell mass from which functional ES cells have been harvested, as reported in the May 2004 Proceedings of the National Academy of Sciences. For the purposes of ANT, *Cdx2* might be deleted from the somatic cell nucleus prior to transfer. Once the partial ES cells have been generated, the gene could be re-installed to allow fully potent ES cells.

This technologically-created limited cellular subsystem, from which the ES cells could be obtained, would fail to establish even the most basic features of human organismal infrastructure. A deficiency at the first differentiation of cell type—the formation of the trophectoderm—means the absence of the most fundamental order. According to Dr. Maureen Condic, a developmental biologist at the University of Utah, "When [the] trophoblast does not form, subsequent development follows a chaotic pattern, suggesting that organismal development has not been 'disrupted' in the absence of [the] trophoblast, but rather that an organism never existed in the first place."

The resulting cells would have no inherent principle of unity, no coherent drive in the direction of the mature human form, and no claim on the moral status due to a developing human life. Rather, such a partial, disorganized organic potential would more rightly be designated a biological "artifact"—a human creation for human ends. The fact that some part of such a constructed entity will carry a certain momentum of development is morally analogous to the fact that we can grow skin in a tissue culture and may one day grow whole organs or limbs in isolation. Lacking crucial elements in its fundamental constitution, such an entity could never rise to the level of a living being.

The scientific prospects for ANT remain largely unexplored, but as stated by Rudolph Jaenisch in testimony to the President's Council, they are within the reach of our current technology.

THE ADVANTAGES OF ANT

Unlike other proposals, ANT would allow a uniquely flexible approach by providing a wide range of ES cell types that would have the full normal complement of human chromosomes, could be of specific genetic types for tissue compatible transplantation, and would not carry the danger of contamination from animal components.

In addition, this technique would offer a far wider range of scientific and medical possibilities than ES cell lines derived from "left over" IVF embryos, including generation of diverse and pre-designed ES cell lineages for disease modeling and pharmaceutical development. Indeed, in allowing controlled and reproducible experiments, ANT might serve as a temporary bridge to transcendent technologies such as direct nuclear reprogramming. Furthermore, in establishing a morally acceptable means for the procurement of ES cells, this important realm of scientific investigation would be opened to federal funding and the advantages of both broad public support and cooperative research collaboration on a national level.

ANT would also unburden ES cell research from the additional ethical concerns of the "left over" IVF embryos, including the attendant clinical and legal complexities in a realm of great personal and social sensitivity. The one remaining link with IVF, the procurement of oocytes, is a subject of intense scientific research and there appear to be several prospects for obtaining eggs without the morally dubious and expensive superovulation of female patients—the specifics of which we can discuss later.

THE PREEMPTIVE NATURE OF ANT

The crucial principle of any technical variation of ANT, however, must be the *preemptive* nature of the intervention. This process *does not* involve the creation of an embryo that is then altered to transform it into a non-embryonic entity. Rather, the proposed genetic alteration is accomplished *ab initio*, the entity is *brought into existence* with a genetic structure insufficient to generate a human embryo. From the beginning and at every point along its development it cannot be designated a living being. If such a limited biological entity were accorded a certain cautionary respect—as with all human tissues—this project would not compromise any funda-

mental moral principles. Moreover, such techniques could be developed using animal models, then confidently extended to work with human cells without engaging in research that involves the destruction of human embryos.

CONCLUSION

The moral distinctions essential to discern and define the categories of organism, embryo and human being will be vital as we go forward with scientific research involving human embryonic stem cells, chimeras, and laboratory studies of fertilization and early embryogenesis. Advances in developmental biology will depend on clarifying these categories and defining the moral boundaries in a way that at once defends human dignity while clearing the path for scientific progress.

At this early stage in our technological control of developing life, we have an opportunity to break the impasse over stem cell research and provide moral guidance for the biotechnology of the future. This may require a constructive refinement of some aspects of moral philosophy, together with creative exploration of scientific possibilities, but any postponement of this process will only deepen the dilemma as we proceed into realms of technological advance unguided by forethought. We must initiate the cooperative dialogue that is essential to frame moral principles that can at once defend human dignity and promote the fullest prospects for scientific progress and its medical applications.

Senator SPECTER. Dr. Hurlbut, when you say if you would choose one stand-alone bill, would that be Specter-Harkin's?

Dr. HURLBUT. I suggest that a range of alternative approaches be set aside. I agree with my colleagues that it should be a range of——

Senator SPECTER. Well, but when you talk one stand-alone bill, what bill are you talking about?

Dr. HURLBUT. I am speaking about a bill that would fund—would provide funding for research to establish these alternative approaches.

Senator SPECTER. Okay. I have not seen that stand-alone bill yet. Dr. Battey, let me commend Dr. Lanza and Dr. Hurlbut for what they are proposing here as an alternative. What the Congress is going to have to make an assessment on, if we can fund them all and move ahead with the wide range of alternatives, as Senator Harkin and I have both said earlier, we think that is a good idea.

Dr. Battey, we know the potential if we remove the limitations now on Federal funding, which have been proposed by Castle-DeGette and Specter-Harkin. How speculative are the proposals by Dr. Lanza and Dr. Hurlbut?

Dr. BATTEY. Mr. Specter, it is always dangerous to make predictions about the future, because science has so many times in the past surprised us. Both proposals, I believe, have lots of technical merit, and even some preliminary data to suggest that they may be possible. In fact, I think it is—the safest thing to say is that science moves forward the fastest when we pursue a whole variety of avenues and approaches towards the generation of pluripotent cells, because I hope my colleagues would agree with me that——

Senator SPECTER. Dr. Battey, we do not have much time. If you had to make a choice among the three alternatives, which would you choose?

Dr. BATTEY. That is a difficult choice to make. I would probably choose to pilot all three in pre-clinical studies and animal models, and go with whichever approach is the most promising.

Senator SPECTER. Dr. Daley, you say that you have written in the——

Senator HARKIN. What three is he talking about?

Senator SPECTER. Senator Harkin wants to know what three you are talking about. I am reluctant to answer his question to you.

Dr. BATTEY. The three proposals in the President's Council on Bioethics, they were endorsed by them, which involved the attempts to create cell lines from embryos that are no longer dividing. Of course, with the Federal funds, all of these would be done initially in animal studies. We have been questioned whether or not we could use Federal funds to study any of these, using human embryos, because of the Dickey provision on the DHHS appropriation.

But anyway, the idea about harvesting cells from embryos that are no longer dividing, altered nuclear transfer, and blastomere harvesting from the eight-cell stage embryo.

Senator SPECTER. Dr. Daley, in your testimony you said that you have written in the scientific journals on Dr. Hurlbut's idea and have found it lacking. Could you amplify that, please?

Dr. DALEY. Yes. I think it is technically feasible. The question is whether it will satisfy all the ethical concerns. As Dr. Lanza said, engineering a gene defect so that you create something which is defective is engineering a defective embryo. There are many conservative thinkers who have argued against this policy.

I wish it were so. I wish we could have an easy technical fix but I am afraid that this will not bring us to consensus. There will still be some who oppose altered nuclear transfer because it creates a defective embryo.

Senator SPECTER. Dr. Lanza, if the Federal funding were limited to either being directed toward your proposal or to the—removing the current limitation, which would you have chosen?

Dr. LANZA. Oh, that is a no-brainer. Removing the current limitations. We need to pass H.R. 810. It is that simple.

Senator SPECTER. So, you would—if it came to an option of your proposal or Specter-Harkin, Castle-DeGette, you would choose to remove the current limitations?

Dr. LANZA. Absolutely. Specter-Harkin. But we will take any additional money you would throw our way.

Senator SPECTER. Dr. Hurlbut, are you going to be as generous with your conclusion as Dr. Lanza?

Dr. LANZA. I will let you decide how generous I am. I believe we should find a way to go forward with our biomedical research that gathers in our whole Nation. The idea of people going to the hospital and having moral problems about the development of their treatment strikes me as a very unhappy prospect. I believe there are ways to go forward where we can go forward with consensus. I think we ought to explore those.

Senator SPECTER. Dr. Hurlbut, we now have a situation, it was noted repeatedly even in this hearing, about 400,000 of these embryos frozen, they are going to be discarded. I, too, would like to find a consensus. But where you have the ideas which you and Dr. Lanza have articulated, as meritorious as they are, and my inclination would be to fund them all, providing there is not a limitation on Specter-Harkin. But how do we come to grips with the very basic objection, which has been raised by one side, that we are destroying a life, when these 400,000 embryos are going to be destroyed if they are not used?

Dr. HURLBUT. Well, I guess that is your dilemma as a legislator. I put forward my proposal in the spirit of healing, to try to be inclusive. I want to say that I respectfully disagree with Senator Harkin. I do believe there is a moral dilemma here.

A large percentage of our population does have moral concerns about the process of desegregating or destroying the human embryo in the procurement of embryotic stem cells. If there are ways to get these cells without the destruction of what many consider a human life in process; and I think biologically it is undeniably a human life; morally, you may make arguments differently.

But if we can go forward without that action, which is apparently prohibited by the Dickey amendment, because even the Castle-DeGette bill does the actual destruction off-site, right? Am I right about that? It does not directly provide NIH funds for the actual active procurement of the cells. That seems to me a direct affirmation of the fact that there is a moral issue there.

Senator SPECTER. Dr. Hurlbut, if Congress were to conclude that we support Dr. Hurlbut and Dr. Lanza, would you endorse Specter-Harkin?

Dr. HURLBUT. I am among those who have moral concerns and believe that the best way for our country to go forward would be to take the time and energy, and I do not believe it would take that long, to explore these alternative methods. And then after that, I think we should revisit the kind of legislation that you are proposing.

Senator SPECTER. So, that is a delayed yes?

Dr. HURLBUT. It is a delayed answer.

Senator SPECTER. All right. Well, then, what is the answer? We are not going to conclude the question without an answer.

Dr. HURLBUT. Senator, are you asking——

Senator SPECTER. I am now under Senator Harkin's time, by the way.

Senator HARKIN. That is okay. You are doing great.

Dr. HURLBUT. Are you asking me if I have——

Senator SPECTER. Well, I am asking essentially, recognizing your preference, and I can understand it, if we could solve all the concerns. But in the context where it is very speculative and uncertain as to whether your idea would work, Dr. Lanza's idea would work, but we do know if we removed the restriction on Federal funding, as Senator Harkin and I have proposed, and Congressman Castle and Congresswoman DeGette have proposed, you can move ahead with embryonic stem cell research.

So, would you foreclose the prospects of scientific advantage by removing the current limitation on Federal funding, which Senator Harkin and I have proposed?

Dr. HURLBUT. At this time, I would favor the pursuit of a way that can go forward without the institutional endorsement of the instrumental use of human embryos. I believe that we, as a society, would be stronger and more coherent, and I also believe it would lead to a better long-term result for the prosperity of our scientific enterprise.

We have sequenced the human genome. We are learning about the proteins that the genes code for, and from here on out, it is developmental biology; living beings. We need to find principles to go

forward. ESL research is just the beginning of a whole series of ethical dilemmas. If we can solve this in a positive way, we can set the frame for going forward.

I think in the long run, instead of a series of battles, we will have a coherent moral platform to guide our science. That is why I put forward the kind of proposal I have done, because I think it would set the moral frame.

Senator SPECTER. Well, you have articulated it accurately. It is going to be a matter of time. You have also articulated accurately it is a legislative judgment and we legislators are prepared to make it. Again, I only have one vote out of a hundred, but I have waited too long now. Eight years is too long to wait for stem cell research.

Dr. Green, how do you evaluate the prospects of success of what Dr. Hurlbut and Dr. Lanza have proposed, contrasted with what we know can happen if we enact Specter-Harkin?

Dr. GREEN. Well, I think there is no question that we could move ahead very quickly if Specter-Harkin is enacted to really moving stem cell research forward in this country. We are losing our ability to do that rapidly. I think there is no "if" here. There is a question of moving ahead or not.

I think these other proposals are speculative. I personally believe that single-cell blastomere biopsy is most acceptable, possibly in an ethical and legal direction, to support.

I do want to say that I have rather grave reservations about altered nuclear transfer as a procedure. I believe that it can properly be characterized as deliberately creating and then destroying an impaired form of human life. I think that people who look more closely, ethically, will agree with that estimate of it.

I think it also opens a slippery slope to the deliberate creation of impaired human beings for transplant purposes. I really do not see the difference between creating an impaired embryo and creating an impaired infant, an infant without a brain as a source of organs for harvest.

So I think of all the proposals that have been put forward, this is the one that raises the most substantial and serious ethical—not simply technical—but ethical questions, whereas the other proposals, I think, are ethically worthwhile, praiseworthy, and should be supported and funded. But above all, I think we should use the methods we currently have to use—to take these cells from embryos that are being destroyed as we talk, by the thousands around the world. This is material—these embryos are being destroyed. They are not being destroyed by governmental officials. They are being destroyed by parents and clinicians. That material is going to waste.

Why should they not be free to donate those cells for further research that saves human life? I think we should characterize it as allowing people to donate cells, from embryos that have been discarded, for lifesaving purposes.

Senator SPECTER. Thank you, Dr. Green.

Senator Harkin?

Senator HARKIN. Thank you. I do have a line of questioning but I see Dr. Hurlbut wanted to respond, so I want to——

Dr. HURLBUT. Thank you. I want to say in response to that, that I put forward my proposal to solve this problem, not to create dis-

abled embryos. I do not think that is a correct scientific analysis of what I am proposing.

I am proposing to create something that has a natural analog. In nature, you have manifestation of certain types of biological developments that are clearly not embryos and yet are capable of producing embryonic stem cells. I think that to label what I am producing or what I am suggesting be produced as a development of a mentally incompetent embryo or inflicting injury on an embryo, is to presume the existence of an embryo in the construction that I make.

That is not what I am going to do. I think that the nature of my proposal is such that one would analyze the science in such a way that you would not produce a unified, coherently operating entity that is the definition of an organism. The fact that, that is reasonable is evident in the statement that accompanies the proposal for oocyte assisted reprogramming, which has the affirmation of a broad range of moral philosophers and religious authorities who have examined it and thought carefully about it.

This proposal really does provide a way forward. It does not create embryos. It creates entities that are non-embryonic. As they used to say about Oakland, there is no there, there. Well, it is the same here. There is no embryo there.

Senator HARKIN. Well, I would just respond that the white paper that the President's Council on Bioethics, page 59, "The third proposal, cell is derived from specially engineered biological artifacts." That is what you are talking about. "Because this proposal raises many serious ethical concerns, we do not believe that it is, at this time, ethically acceptable for trials of human material. Although a few of us are not eager to endorse even animal and other laboratory work investigating potentially human applications, most of us believe the proposal offers enough promise to justify animal experimentation, both to offer proof of feasibility and utility and to get evidence bearing on some of the ethical issues." So, that is just from the President's Council regarding the altered nuclear transfer system.

I guess, Dr. Hurlbut, since we are talking about this, you went to Stanford; they teach logic at Stanford, I am sure. If "A" equals "B," and "B" equals "C," "A" must equal "C." So, let us start with that for logic.

Are you morally opposed to in vitro fertilization? A simple question.

Dr. HURLBUT. I think we are all troubled by the fact that in vitro fertilization creates more embryos than it implants, and we would all like to seek a way to not do that. Beyond that I feel like it is a therapeutic intervention against a disorder, and in that sense I think it should be a procedure that is within the spectrum of personal choice and reproductive options.

Senator HARKIN. So, you believe that if a couple wants to pursue in vitro fertilization they should be allowed to do so?

Dr. HURLBUT. You know, when that issue——

Senator HARKIN. I do not mean to debate this. I am just asking you a simple question.

Dr. HURLBUT. The simple question is: Should they be allowed——

Senator HARKIN. Yes.

Dr. HURLBUT [continuing]. To do so?

Senator HARKIN. Should they be prohibited?

Dr. HURLBUT. Given the fact that it is a private reproductive choice and is not the institutional endorsement with Federal funds, I think it is in a different category. If I were a legislator I would make it legal.

Senator HARKIN. I take from that, that you are not morally objecting to in vitro fertilization. If you are morally objecting, you would be objecting to whether it was private or public, right?

Dr. HURLBUT. I am morally troubled by the creation of human embryos that are not implanted. That dimension of in vitro fertilization, I have moral concerns about.

Senator HARKIN. Well, I am still trying to figure out what that means. I am troubled by a lot of things in life. I mean a lot of things trouble me, but I do not find them totally objectionable, or that I want to impose some control, or something. I just happen to find them troubling.

What I am trying to get to is if (A) you do not find in vitro fertilization morally objectionable, private or public, whatever, by the very fact that you have IBF, you are going to create surplus embryos. That is a fact on which we can all agree, therefore, that is (B). Therefore, (C), if you believe that in vitro fertilization is okay, and it is morally all right for couples to pursue, then you are (C) going to have excess embryos.

Dr. HURLBUT. Senator Harkin——

Senator HARKIN. Am I wrong in that logic?

Dr. HURLBUT. Yes, you are.

Senator HARKIN. Oh. Tell me where I am wrong in that logic.

Dr. HURLBUT. There are at least two countries in the world, Italy and Germany that do not allow the creation of excess embryos but do allow IBF.

Senator HARKIN. What do they do with the excess embryos?

Dr. DALEY. That is true, but their success rates for assisted reproduction are dramatically less than in the United States.

Dr. HURLBUT. Well, because they do not have all of the ones to draw from.

Dr. DALEY. Right.

Senator HARKIN. So, again, I do not understand why, if you create excess embryos, which we do, 400,000 we estimate here, and they are going to be destroyed—you agree with that, right, Dr. Hurlbut? They are going to be destroyed. They are being destroyed every day, right now, as we sit here; they are being destroyed every day.

Dr. HURLBUT. There are an estimated 400,000 frozen embryos in the United States whose fate is currently uncertain. Only 11,000 of those have specifically been designated for research. Of those, many of them would not qualify under the informed consent rules. The estimates are that we might get a couple hundred lines out of those.

I do not disagree that we could fast forward to the science with new lines. I have never taken the position that embryonic stem cell research is not necessary in the positive sense of interesting exploration. We must acknowledge, of course, that it is speculative re-

search; it is not absolutely proven. But I am with George Daley with this. I think we should try to find ways to go forward.

I am concerned that we find a way to go forward that is encompassing, that includes the diversity of moral opinions in our society. That is——

Senator HARKIN. Well, now——

Dr. HURLBUT. But I do not it is just simple logic. I think it is the art of governing a society.

Senator HARKIN. That is the position I think that Senator Specter and I have taken. That is these are all worthy of investigations. We have all said that. We have been saying that for a long time. But what is happening is that there are forces out there now that want to stop the Specter-Harkin bill and shift it only to these other things, which, as we know, have never been done in humans. There have been no trials; they are speculative. Even your own approach, as Dr. Kass said, it raises ethical concerns.

I mean, if it is not an embryo, what is this sort of Frankenstein-thing that we are creating by taking the gene out? What is it called? What is it, if it is not an embryo? I do not know what it is.

Dr. HURLBUT. We are going to have many questions like this as we——

Senator HARKIN. Sure.

Dr. HURLBUT [continuing]. Go forward in the future. As I said, we are in the era of development biology. Someday we will probably be able to develop human organs in factories. That immediately seems gruesome to us, but on the other hand it could be very positive. The moral issues are going to be very challenging and we need to find a frame to go forward with them.

Senator HARKIN. Well, I——

Senator SPECTER. Senator Harkin, may I interrupt you for just 1 minute?

Senator HARKIN. Yes.

Senator SPECTER. Regrettably, I have some duties on the Judiciary Committee and I am going to have to excuse myself at this point. I am going to leave you with Senator Harkin all alone.

Senator HARKIN. I only have a couple more questions.

Senator SPECTER. Before I go, I want to thank you for coming here today. I want to thank you for what you are doing. We have had—this is our 16 hearing. I think this has been our best, really, on the specifics as to what we are getting into.

It may be that Senator Harkin and I understand more because we have been educated over a long period of time. And it takes a long period of time to educate us. But what you have done, Dr. Hurlbut, and what you have done, Dr. Lanza, we admire, in seeking another alternative.

The dialogue that Dr. Hurlbut and Senator Harkin have had is very illuminating and shows the depth and intensity of the problem. We have taken the lead on putting up a lot of money; $28 billion is a lot of money for NIH. It is not enough, but it is a lot.

We did not have a chance to get into what stem cells can do. We have done that at other hearings. We have had words from the directors of NIH as to the great potential, and so many, many lines. I think it is summed up in what Dr. Kass said when he—in his op-

ed piece he said, "It is too early to know which of these approaches will prove most successful." But we do know that if you have Specter-Harkin and the Castle bill, you can move ahead promptly in a very, very important line.

I will be backing all the research and using this subcommittee as the leveraging factor to lead the Congress to more money for the scientific research. I do regret that I have to go, but we have a lot of conflicting demands on us here. The Judiciary Committee, as I know you see, is a very heavy one.

I have turned the gavel over to Senator Harkin before, and it has worked out very well.

Senator SPECTER. Thank you all very much.

Tom, it is yours.

Senator HARKIN [presiding]. Thank you, Mr. Chairman. Dr. Lanza——

Dr. LANZA. Yes?

Senator HARKIN [continuing]. Just to reiterate, your blastomere extraction technique has been successful only in mice, so far as I understand it?

Dr. LANZA. That is correct.

Senator HARKIN. How long do you think it would take before you could achieve the same success in humans?

Dr. LANZA. Well, obviously, that is an impossible question to answer. It could be a few years, it could take a decade. Until you do the research, you simply do not have that answer.

Senator HARKIN. We just do not know?

Dr. LANZA. We do not know, no.

Senator HARKIN. Dr. Daley, again, for the record, some opponents of the Specter-Harkin bill, or H.R. 810 or S. 471, say that instead of lifting the current restrictions on stem cell research, we should focus entirely—well, either on three or four. I am a little confused. I thought there were four, and then I heard three. So it is either three or four unproven alternatives.

Do you think this makes sense, from a scientific perspective?

Dr. DALEY. No. No. Absolutely not. No. I think that support for the speculative proposals that are being considered, instead of support for expanded access to embryonic stem cell lines, which we have available to us, and we already know are powerfully and vitally critical to medical research, is really a vote to delay important medical research. So, I do not think we should be keeping the scientific community or the patient community waiting.

Senator HARKIN. Address yourself to this question. If we had the approach—I want to phrase this correctly. If we had an approach that only focused on these alternative methods, but did not allow the current restriction on Federal funding of research on stem cell lines, H.R. 810 or S. 471, lifting that restriction, if we just focused on the alternative methods without lifting the present restrictions, would that delay our ability to find cures and treatments for diseases like juvenile diabetes, or Parkinson's, or ALS?

Dr. DALEY. Yes. I mean, it essentially puts us in the same unfortunate position we are in today, which is working with a small set of presidential cell lines, cell lines that do not provide us models for human diseases, do not allow us to do some of the most medically forms of research, do not allow us to take advantage of the

hundreds of newer versions of cell lines. Cell lines that have been derived in the absence of mouse feeders, free of mouse contamination. Cell lines that model human disease. Customized patient-specific cell lines.

Without Senate passage of H.R. 810 and without expanding access to these lines, we are in the same terrible position. So, I do not think that these alternatives solve the problem in any way. I think they are a quixotic attempt to divert us from the central task of expanded access to embryonic stem cells.

Senator HARKIN. Dr. Green, same question.

Dr. GREEN. Yes. I very much agree with what Dr. Daley has just said. I would add to that the peculiarity that even if these approaches proved technically acceptable, there are profound ethical questions at the other side of them. People would look at altered nuclear transfer and raise some of the questions I did. They might ask questions about safety, about the biopsy technique. They would worry about the inducement to cloning in some of these technologies.

So we could be going ahead on these technologies and find that many of the people who are currently opposed to the expansion of stem cell lines have as many objections, or more objections, actually, to these techniques than they do even to embryonic stem cell derivation now.

Senator HARKIN. I am going to work this around here. I am not—the question that I posed, and I am going to ask you is: By just focusing on the alternative methods, but keeping the present lid on the restrictions, keeping the present restrictions in place, would that delay the ability find cures and treatments for disease like juvenile diabetes, Parkinson's, and ALS? Both of you responded yes. Dr. Hurlbut, what say you?

Dr. HURLBUT. Would it delay——

Senator HARKIN. Okay. I will reiterate my question.

Dr. HURLBUT. Yes. I understand it. There is no question but that you can go forward faster with science if you do not take—do not have concerns about research subjects and a variety of moral issues. The point is that you can move ahead scientifically, but at the same time be moving backwards in terms of social consensus and social support of science, and you can be moving backwards in terms of the moral foundations of our civilization. We are at a hinge of history here. We need to take the time to get this right, to open the future of science in a positive way that does not have constant conflict.

Let me say something and I do not raise this in the spirit of negativity or hysteria, and certainly not to encourage anything related to this. But a Stanford we have our animal research facility hidden under a parking lot, because there are the animal activists, animal rights activists.

I just keep asking myself, where is the embryo facility going to have to be handled? Where is that going to be hidden? When so many Americans feel so strongly about this. Could we not, in the spirit of unity, engage in the constructive conversation and the positive creative use of our scientific tools to find an answer to this?

I agree with Dr. Green. It is challenging. There are difficult ethical issues. But just as there are difficult scientific issues that we will have to solve, we can solve these difficult ethical issues, too, if we put our minds together and seek national unity to do so. I favor the science, but I also favor the moral frame for the science.

Dr. LANZA. I think what we are hearing is that——

Senator HARKIN. Now, I want to stick on this question. So one, two, three of you have answered positively. Dr. Lanza.

Dr. LANZA. I think there is a very real human tragedy out there and we need to move ahead with this ASAP. I think that the field of stem cell research has been crippled by the lack of accessibility to quality stem cell lines. So, again, I think there is no question.

Senator HARKIN. Dr. Battey. Do I need to repeat my question?

Dr. BATTEY. No. Unlike my four colleagues, I am a member of the executive branch of the Government. As you know, Senator, I cannot comment directly on pending legislation. I am prohibited by law from doing that. But I can say that there is no scientist that I know that would argue that more cell lines would not accelerate the pace of research.

Comments have been made about disease-specific cell lines, about, you know, designer cell lines, about cell lines that have been derived under different conditions than were extant at the time that Jamie Thomson wrote his first paper. All of these cell lines offer scientific opportunities that are right now beyond the reach of Federal funds. That I can say.

Senator HARKIN. Let me just say, try to bring this to a close. There are many people in our country who find in vitro fertilization morally unacceptable. But should that be the controlling factor, or should it be allowed for them to personally be opposed and not to engage in it themselves?

I do not know where it becomes the tilt. At what percentage does it become all right, acceptable, to pursue a certain line of scientific inquiry based upon polling data? Is it 60 percent? Is it 70? Is it 75? Is it 82? Is it 83.5? Where does it tilt? How do people know?

I can only tell you from my own experience of traveling around Iowa and talking about this issue in front of audiences, that when I talked about it, people said, "Wait a second. That is not what I thought. That is not what I was thinking about."

I will say this publicly, there has been a concerted effort by many, maybe because they find it morally objectionable, I do not know, maybe there are some politics, it could be all kinds of reasons out there, but some people have really tried to confuse this issue by equating an embryo to a fetus.

There are many people who believe that what we are talking about is a fetus. When the debate was on the House floor, a certain Congressman talked about, and I heard the debate, talked about—and it was replayed again on CNN, talked about we cannot be engaging in dismembering human life to provide parts and stuff for others. That was played on CNN.

CNN then put up a picture of a fetus on the screen. And so there are a lot of people out there that do not know. They think in their mind that when we are talking about embryotic stem cell research, they are thinking of fetuses. I know this for a fact.

So that, every time I do my little thing and hold it up and say what I have here, I said that is what we are talking about. That is how big the embryo is. It is as big as a period at the end of a sentence. It has what, eight—how many cells does it have? Eight? Thirty? Less than a 100 cells. I do not know. I get confused how many cells.

People do not realize—they do not get that. They finally say—and I have had people come up to me and say, "I did not realize—I thought—I thought we were talking about a fetus."

So, I think that the more that knowledge gets out and the more information that gets out about exactly what we are talking about, how many cells we are talking about, and the fact that this is not a fetus, people then begin to say, "Well, then maybe I will change my thinking on this. Maybe I will think differently on this."

So, it has to do—I guess my point is, is knowledge, information that is scientifically pure as possible and not biased one way or the other that gets out there. I think that, what is it, around 60 percent that support it now, will probably go even higher.

So, do we want 100 percent? Do we have to wait until every single person in this country agrees that something is not morally objectionable? We will never get there; that will never happen. So somehow, we have to find a way of encompassing as broad a consensus as possible. But to do it, I think, as best as we can, an intellectually honest approach, as to how we go about this.

I think that the more information that gets out on embryonic stem cell research, whether it is National Geographic, with their issue, or Parade magazine, or Newsweek, or Time, or articles that are written about it, the more people that are reading about it, the more people who begin to understand it, the more support it gets for lifting these restrictions. Therefore, the moral objections fall away.

Now there will always be some who are morally objectionable on religious grounds, ethical grounds, whatever. Basically, religious, more than anything. I understand that. There are religious objectives to, as I said earlier, artificial contraception. There are religious—strong religious objections in certain religions. Well, that is fine. But I do not know that—that ought to be the controlling factor in our society.

So, again, we were talking about moving ahead in a way that gathers in the nation, one of you said that, I do not know who it was, gathers in the whole nation. Well, how long do we wait? Do we wait until it is 100 percent or not, or do we try to make science-based judgments that are at least morally acceptable to the vast majority of people in this country? It seems to me that is our system, and that is the way we ought to move ahead in this regard.

There are people out there that suffer. People that have illnesses and diseases. I do not know whether this is going to work or not, but I think we ought to try it. We ought to move ahead in it. All these other approaches, even Dr. Hurlbut's, sure, I think we ought to pursue it. I think we ought to look at it. I have no problems with any of this stuff. I think there are certain ethical problems with all of these, as people may raise.

But I am all for opening—I have always said basic research, Dr. Battey, to me, has always been like opening doors. You do not

know what is behind them. That is basic research. That is why I have always said—people have said, well, you spend all this money on basic research and nothing comes of it. I said, "Well, that is basic research."

If you have 10 doors, and you are only going to open 1 door, the odds against finding your answer is pretty high. If you open five doors, it gets better. Seven doors, better. Eight doors, better. Once in a while you strike it lucky. Once in a while you open one door and you do strike it lucky.

Dr. BATTEY. That is why we call it research and not engineering, Senator.

Senator HARKIN. That is research. So like I said, with all these things, I have no problems with that, and moving ahead on it.

But I came back to where Senator Specter was, I do not mean to speak for him, but—and those of us who are supporting lifting the restrictions, do not stop this. Let us move ahead on it aggressively. Let us go ahead and investigate these other alternatives. Maybe one of them may even prove superior on down the road someplace. We do not know that.

But we do know this one. Extracting embryonic stem cells from in vitro fertilization that are going to be destroyed under the ethical guidelines that we have constructed, informed consent, no money, and exchange hands, cannot be paid for, and third, can only be used for stem cell extraction, cannot be implanted. I think pretty good ethical guidelines and this is the way we ought to move ahead on this.

Then if we want to bring up these other bills to find other alternative approaches, I will be first in line in voting and supporting for the funding for these alternative approaches. But to say to so many people who are suffering today, and children who are pinning their hopes on this, and that—and each one of you, every single one of you have said, in answer to my question, that it would delay our ability to find cures and treatments for disease like juvenile diabetes, Parkinson's, and ALS. You answered yes; it would delay it, if we do not lift the restrictions.

So, to me, aside from the ethical or moral problems that some people have with it, and I understand that, the fact remains that the best approach that we know of right now, scientifically, to find the cures for these things, like juvenile diabetes, and Parkinson's, and ALS, and spinal cord injuries, is through embryonic stem cell derivation and research. That is why we have to move ahead.

ADDITIONAL STATEMENTS

This material was receivd by the committee for the hearing record.

[The statements follows:]

PREPARED STATEMENT OF JOYCE FRYE, NCCAM POST-DOCTORAL RESEARCH FELLOW, CENTER FOR CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS

Senator Specter: Thirteen years ago, my 12 year old son was cured of Acute Renal Failure (Nephrotic Syndrome) with homeopathic medicine in what his pediatric nephrologist at Thomas Jefferson University Hospital described as a "miracle". He has had no further health issues and is now an Olympic aspirant in figure skating as an ice dancer. Since his amazing recovery, I have devoted my medical career to learning the art and science of homeopathy and attempting to do research in it. I

am now blessed with the opportunity to further that aspiration as a post-doctoral fellow in the Center for Clinical Epidemiology and Biostatistics at UPenn, receiving a stipend for my research education from NCCAM. I have also served as the president of the National Center for Homeopathy and am currently the president of the American Institute of Homeopathy—the nation's oldest medical organization founded in 1844.

However, NCCAM has yet to issue any funding specifically for homeopathy, and the CDC continues to ignore homeopathy as a potential response for emerging infections despite homeopathy's 200 year history of success in epidemics, especially the 1918 Spanish flu pandemic where mortality rates under homeopathic treatment were in the range of 1 percent. Additionally, homeopathic practitioners on site in the Bali explosions and who have responded to Tsunami relief have hundreds of anecdotes of rapid and amazing responses to homeopathic care. It is troubling to watch events such as the London bombings knowing that it can happen in the United States again and that our trauma could could be substantially diminished if first responders were able to use a few simple and inexpensive homeopathic medicines.

To that end, I hope that you will support a fiscal year 2006 NIH budget of $30.6 billion, an increase of 6 percent over the President's request, and insert or support language drafted by a committee of the National Center for Homeopathy in the Labor, HHS, and Education appropriations bill, which is attached.

Thank you for all of your hard work for Pennsylvania and for the Nation, and wishing you a speedy recovery from your personal health challenges.

FUNDING REQUEST OF THE NATIONAL CENTER FOR HOMEOPATHY

To explore the potential use of homeopathic medicine for protection against and treatment of agents of chemical and biological warfare, for underserved populations, and for emerging infections, $16.5 million for 3 years to be used for:

—Homeland security Homeopathic Emergency Response Training (HERT) by the National Center for Homeopathy teaching homeopathic protocols for response to trauma and bio-terror in 10 HERT sessions located in strategically important regions of the United States, each training session to be marketed to and open to physicians and the general public.

—Preparation and testing of Ultra High Dilution (UHD) forms of agents of potential chemical and biological warfare for prophylaxis against and treatment of injuries resulting from exposure to said agents.

—NIH Program announcement and directed funding for research specific to homeopathy including funding for research in mechanism of action and long-term longitudinal studies

—Educational projects for self-care in underserved populations, for utilization of urgent care facilities among users of homeopathy for self-care, for use of telemedicine in rural populations, for general health and absenteeism in occupational medicine and worker's compensation clinics

—Inclusion of experienced homeopathic practitioners in CDC evaluation of emerging infections both in the United States and abroad.

PRODUCTION OF PLURIPOTENT STEM CELLS BY OOCYTE ASSISTED REPROGRAMMING

JOINT STATEMENT

As described in the President's Council on Bioethics' recent White Paper, altered nuclear transfer (ANT) is a broad conceptual proposal for producing pluripotent stem cells without creating and destroying embryos. In the description set forth below, we outline a research program for a form of ANT that should allow us to produce pluripotent stem cells without creating or destroying human embryos and without producing an entity that undergoes or mimics embryonic development. The method of alteration here proposed (oocyte assisted reprogramming) would immediately produce a cell with positive characteristics and a type of organization that from the beginning would be clearly and unambiguously distinct from, and incompatible with, those of an embryo. Incapable of being or becoming an embryo, the cell produced would itself be a pluripotent cell that could be cultured to establish a pluripotent stem cell line. Significantly, this cell would not be totipotent, as a zygote is.

Our proposal is for initial research using only nonhuman animal cells. If, but only if, such research establishes beyond a reasonable doubt that oocyte assisted reprogramming can reliably be used to produce pluripotent stem cells without creating embryos, would we support research on human cells.

With few exceptions all human cells contain a complete human genome, i.e. the complete DNA sequence characteristic of the human species. Specifically, one-celled human embryos, pluripotent human embryonic stem (or ES) cells, multipotent human adult stem cells, and differentiated (specialized) adult human cells such as neurons all contain a complete human genome. Thus, possession of a human genome is a necessary but not sufficient condition for defining a human embryo with its inherent dignity. Rather the nature of each cell depends on its epigenetic state, i.e. which subset of the approximately thirty thousand human genes is switched on or off and, if on, at what level. For example, the gene for albumin, a liver specific protein, is found both in human embryos and in adult human liver cells called hepatocytes. However, neither the messenger RNA (mRNA) for albumin nor the protein itself is found in single-celled embryos because in them the gene is silenced.

This fundamental observation has given rise to the concepts of cell fate plasticity and epigenetic "reprogramming." If successful, reprogramming converts a cell from one kind to another by changing its epigenetic state. The ability to clone animals, such as Dolly the sheep, by transfer of a specialized adult nucleus to an enucleated oocyte demonstrates the power of epigenetic reprogramming: the oocyte cytoplasm is sufficient to reprogram the somatic nucleus to a totipotent state. Human cloning has been proposed as a means of generating human embryos whose pluripotent stem cells would be used in scientific and medical research. Here, through a form of altered nuclear transfer, we propose to utilize the power of epigenetic reprogramming in combination with controlled alterations in gene expression to directly produce pluripotent cells using adult somatic nuclei, without generating and subsequently destroying embryos.

How do pluripotent stem cells differ from totipotent single-celled embryos? Several key transcription factors essential for establishing and maintaining the pluripotent behavior of ES cells have been identified. Importantly, some of these are specifically expressed only in pluripotent cells, such as embryonic stem cells or the cells found in the inner-cell-mass (ICM) of the week-old embryo or blastocyst. They are not expressed in oocytes or single-celled embryos. Expression of these factors therefore positively defines and distinguishes mere pluripotent cells from embryos. These factors instruct a cell to have the identity of a pluripotent cell. Currently, the best studied example is the homeodomain transcription factor called nanog (Mitsui, Tokuzawa et al. 2003). Nanog is not present in oocytes or single celled embryos, but first becomes expressed weakly in the morula and then highly in the ICM (Mitsui, Tokuzawa et al. 2003; Hatano, Tada et al. 2005). Deletion of nanog does not prevent early cleavage stages of embryogenesis including formation of the ICM but does prevent the formation of an epiblast (Mitsui, Tokuzawa et al. 2003). ES cells in which nanog is blocked lose their pluripotency—which clearly shows that nanog is a positive factor instructing cells to be pluripotent, i.e. to behave like an ES cell. Furthermore, ES cells which constitutively express nanog can no longer be differentiated, i.e. are forced to remain in their undifferentiated state (Mitsui, Tokuzawa et al. 2003).

We propose a procedure that combines epigenetic reprogramming of a somatic nucleus with forced expression of transcription factors characteristic of embryonic stem cells, to produce a pluripotent stem cell. As a result of this procedure, nanog and/or other, similar factors,[1] would be expressed at high levels in somatic cells prior to nuclear transfer, to bias the somatic nucleus towards a pluripotent stem cell state. Such altered nuclei would then be epigenetically reprogrammed by transplantation into enucleated oocytes. Alternatively or concomitantly, the mRNA for these same factors could be introduced into the oocyte prior to nuclear transfer. This procedure could ensure that the epigenetic state of the resulting single cell would immediately be different from that of an embryo and like that of a pluripotent stem cell: the somatic-cell nucleus would be formed into a pluripotent stem-cell nucleus and never pass through an embryonic stage. Therefore, unlike some other proposed methods of ANT, this method would achieve its objective not by a gene deletion that precludes embryonic organization in the cell produced, but rather by a positive transformation that generates, ab initio, a cell with the distinctive molecular characteristics and developmental behavior of a pluripotent cell, not a totipotent embryo. This should allow us to produce a pluripotent stem cell line with controlled genetic characteristics.

[1] Nanog is only one example of a growing list of candidate factors, numbering probably at least 10. Oct3/4 is another well-studied example (3) and is noteworthy because it is also expressed at high levels in pluripotent adult stem cells.

REFERENCES CITED (WITH ABSTRACTS)

Hatano, S. Y., M. Tada, et al. (2005). "Pluripotential competence of cells associated with Nanog activity." Mech Dev 122(1): 67–79.

Nanog is a novel pluripotential cell-specific gene that plays a crucial role in maintaining the undifferentiated state of early postimplantation embryos and embryonic stem (ES) cells. We have explored the expression pattern and function of Nanog and a Nanog-homologue, Nanog-ps1. Nanog-ps1 was mapped on Chromosome 7 and shown to be a pseudogene. Immunocytochemical analysis in vivo showed that the NANOG protein was absent in unfertilized oocytes, and was detected in cells of morula-stage embryos, the inner cell mass of blastocysts and the epiblast of E6.5 and E7.5 embryos, but not in primordial germ cells of early postimplantation embryos. In monkey and human ES cells, NANOG expression was restricted to undifferentiated cells. Furthermore, reactivation of the somatic cell-derived Nanog was tightly linked with nuclear reprogramming induced by cell hybridization with ES cells and by nuclear transplantation into enucleated oocytes. Notably, mouse Nanog (+/−) ES cells, which produced approximately half the amount of NANOG produced by wild-type ES cells, readily differentiated to multi-lineage cells in culture medium including LIF. The labile undifferentiated state was fully rescued by constitutive expression of exogenous Nanog. Thus, the activity of Nanog is tightly correlated with an undifferentiated state of cells even in nuclear reprogrammed somatic cells. Nanog may function as a key regulator for sustaining pluripotency in a dose-dependent manner.

Mitsui, K., Y. Tokuzawa, et al. (2003). "The homeoprotein Nanog is required for maintenance of pluripotency in mouse epiblast and ES cells." Cell 113(5): 631–42.

Embryonic stem (ES) cells derived from the inner cell mass (ICM) of blastocysts grow infinitely while maintaining pluripotency. Leukemia inhibitory factor (LIF) can maintain self-renewal of mouse ES cells through activation of Stat3. However, LIF/Stat3 is dispensable for maintenance of ICM and human ES cells, suggesting that the pathway is not fundamental for pluripotency. In search of a critical factor(s) that underlies pluripotency in both ICM and ES cells, we performed in silico differential display and identified several genes specifically expressed in mouse ES cells and preimplantation embryos. We found that one of them, encoding the homeoprotein Nanog, was capable of maintaining ES cell self-renewal independently of LIF/Stat3. Nanog-deficient ICM failed to generate epiblast and only produced parietal endoderm-like cells. Nanog-deficient ES cells lost pluripotency and differentiated into extraembryonic endoderm lineage. These data demonstrate that Nanog is a critical factor underlying pluripotency in both ICM and ES cells.

ENDORSERS

Institutional affiliations are provided for purposes of identification only and do not necessarily represent the views of organizations with which endorsers are affiliated. Endorsers who are not themselves specialists in biomedical science do not put themselves forward as experts in that field. Their endorsement of the proposal pertains to the ethics of ANT–OAR, assuming its technical feasibility.

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CONCLUSION OF HEARING

Senator HARKIN. With that, again, I will join with Senator Specter in saying that this was a very good panel and we thank you very much. I thank you for what you are all doing in your individual capacities to try to find our way through this maze, and thank you for being here today. Please keep up your good work.

Thank you all very much for being here. That concludes the hearing.

[Whereupon, at 11:08 a.m., Tuesday, July 12, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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