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STEM CELL RESEARCH

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

ONE HUNDRED FIFTH CONGRESS

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STEM CELL RESEARCH

WEDNESDAY, DECEMBER 2, 1998

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

The subcommittee met at 9:34 a.m., in room SD–192, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter and Harkin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF HAROLD VARMUS, M.D., DIRECTOR

OPENING REMARKS OF SENATOR SPECTER

Senator SPECTER. The Subcommittee on Labor, Health and Human Services, and Education will now proceed.

Senator Harkin and I discussed our agenda for the year several weeks ago and jointly decided that our initial hearing ought to be on the highly charged, very important subject about the use of human embryos and fetal tissue for medical research and have accordingly scheduled this hearing today.

Before proceeding to the hearing, just a word or two about reports of my own consideration for changing chairmanships of subcommittees. I will be remaining as chairman of the Subcommittee on Labor, Health and Human Services, and Education. I had given some brief consideration to a change. I was surprised, flattered, to hear so many people say that I should stay.

These rumors have a way of appearing in print and sort of out of control. But to put that matter to rest, I shall be remaining as chairman of this subcommittee.

The subject matter on our hearing today arises from a provision of the legislation reported out by this subcommittee last year, which limits the use of Federal funds for research on human embryos. That is an issue which has come into sharp focus with very dramatic recent medical developments, warranting a closer analysis or perhaps a reanalysis of that question.

There is a curious dichotomy, really an inconsistency or an arguable inconsistency, when Federal funds may be used on research on fetal tissue, but not on human embryos. While there are very substantial differences, the question is raised as to whether that is a consistent policy.

The recent advances have shown that the stem cells have potential to grow into any kind of bodily tissue and have, at least reportedly, enormous potential on a wide variety of very serious ailments—heart disease, diabetes, Alzheimer's, cancer, spinal cord. We will get into a full range as we hear from our expert witnesses today.

The problems with embryos are unique because the embryo has the potential to create a new person under some circumstances, and we shall explore that. There has been consideration raised about the use of discarded embryos where couples using fertility treatment discard embryos, another very complex and controversial and very highly charged subject.

The discussion which we will be initiating today, or carrying forward today, is one which will challenge ethicists and theologians as well as Senators and members of the House. The collateral question arises as to whether these procedures may be patented. Some applications have already been made for patents. So there are many, many questions which are raised on this very, very important subject because of the potential to treat illnesses of enormous importance and whether this is an appropriate procedure.

That in a very brief statement, is an outline of some of our parameters which we will expand during the course of today's hearing and beyond. I now turn to my distinguished colleague, the ranking member, Senator Harkin.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Mr. Chairman, thank you very much for your leadership of this committee. Thank you for holding this important hearing to air the ethical and scientific issues involved in stem cell research. I am pleased to have this opportunity to hear directly from Dr. Varmus, our lead-off witness, the distinguished scientists who have conducted this ground-breaking research, as well as from the ethicists who have examined the moral implications.

While the press has highlighted the exciting potential benefits of Dr. Thomson and Dr. Gearhart's work, they have spent much of their time documenting the controversy surrounding their accomplishments. They have focused on the Federal ban on human embryos research, the ethical implications of advanced cell technologies research with human and bovine cells, the President's request to the National Bioethics Advisory Commission, and the scientific furor over the release of ACT's unpublished research to the New York Times.

All of these issues deserve a full debate, and again I thank you, Mr. Chairman, for bringing us together today. I also want to thank you for continuing on and staying as chairman of this subcommittee. I had heard these rumors and I thought if they got very serious I was going to threaten you with great bodily harm if you decided to leave. So I am grateful that you did stay.

Senator SPECTER. That kind of bodily harm might not be cured by stem cells, either. [Laughter.]

Senator HARKIN. They would have to hurry up the research.

I want to thank Dr. West for his commitment to a public discussion of the ethical implications of stem cells research and to commend Doctors Thomson and Gearhart for their groundbreaking ac-

complishments. From enabling the development of cell and tissue transplantation to improving and accelerating pharmaceutical research and development, to increasing our understanding of human development and cancer biology, the potential benefits of this work are awe-inspiring. The cell lines they have isolated and kept alive could reduce the demand for organ donors and pave the way for many life-saving therapies.

They could help pharmaceutical companies improve the testing of their products by providing an unlimited quantity of normal human cells of any tissue. Therefore, rather than going directly from animal testing to human testing, they could test these new drugs for benefits and adverse effects on normal human tissue.

And undoubtedly, a long-term benefit if their work will be to enhance our understanding of human development, as scientists may now be able to produce cells at specific stages of human development that have previously been inaccessible to research.

But all of these benefits could be delayed or even denied to patients without a healthy partnership between the private sector and the Federal Government. As many of you know, Senator Specter and I are strong supporters of this partnership, and we were pleased to be able to provide an historic increase for NIH in this year's budget and will continue to work to double the NIH budget in the next few years.

Now, while the market interest in stem cell technology is strong and private companies will continue to fund the research, the Government has an important role to play in supporting the basic and applied science that underpins these technologies. The problem is that early basic science is always going to be underfunded by the private sector because this type of research does not get products to the market quickly enough.

The only way to ensure that this research is conducted is to allow NIH to support it. But unfortunately, as the American Society for Cell Biology writes in a recent letter, the ban on human embryo research ''has the effect of excluding the majority of the Nation's most prominent researchers who are supported by the NIH and limits the development of new therapies.''

The key question that I hope will be addressed today is whether under current law scientists can use Dr. Thomson's stem cells for federally funded research. These stem cells do not have the capacity to become a human being and, therefore, it is my opinion, based upon a lot of study of this, that they do not fall under the ban on human embryo research.

I know that NIH has asked the general counsel at the Department to examine the law and make a determination. It is my hope that this research will be allowed to go forward.

I would like to point out that Federal support is critical to ensure that stem cell research using human embryos is monitored and that consistent, up to date ethical guidelines are followed. The research conducted by the distinguished scientists sitting before us today holds such hope and such potential for millions of people around the world who are sick and in pain that I believe it is morally wrong for us to prevent or delay our world-class scientists from building on this progress.

However, I think it is right and proper for us as policymakers to consider the ethical implications and demand that consistent, up to date ethical and scientific guidelines are established and followed.

We reach, I think, in the final analysis, the age-old question: What are the limits of human knowledge? I have responded consistently that I do not believe there are any limits to human knowledge. There are ethical limits that society may place on the use of that human knowledge.

But to limit this kind of research and to limit this kind of expansion of human knowledge I believe in the final analysis is really unhuman. As long as the research is conducted in an ethically validated manner, it should be allowed to go forward and it should receive Federal support.

Thank you, Mr. Chairman.

Senator SPECTER. Thank you very much, Senator Harkin.

In accordance with our regular practice, the 5-minute rule will apply for opening statements by each witness. There will be substantial time for questions and answers to elaborate upon positions taken.

SUMMARY STATEMENT OF DR. HAROLD VARMUS

Senator SPECTER. Our lead witness is the distinguished Director of the National Institutes of Health, Dr. Harold Varmus, who has been at the job since November 1993, passing the 5-year mark. At the University of California at San Francisco he earned the Nobel Prize for his work on the causative link between certain genes and cancer. A graduate of Amherst, Harvard, and the Columbia Medical School.

Again, Dr. Varmus, we welcome you and the floor is yours.

Dr. VARMUS. Mr. Chairman and Senator Harkin: Thank you very much.

First let me express on behalf of the biomedical research community and indeed the entire public our pleasure with your official decision to remain as chairman of this committee. The team you have formed with Senator Harkin here has been truly extraordinary and the biomedical research community is extremely grateful for your continued support.

I am also very pleased that you are holding this hearing——

Senator SPECTER. Did you like the $2 billion increase last year? [Laughter.]

Dr. VARMUS. We did, Senator, and we plan to use it well.

Senator SPECTER. We have quite a number of chairs where staff sits. We have a lot of people standing. You are welcome to come up and sit in these green chairs along the sidelines on both sides. It should accommodate another 20 people. And you may even sit in the first four seats on the Senators' dais, to be replaced if you do not have an election certificate or if a person arrives with a Senate election certificate. But you are welcome to take the seats because of the overflow arrangements.

Dr. VARMUS. Will these arrangements be subtracted from my time, Senator?

Senator SPECTER. Yes.

Dr. VARMUS. Thank you.

Senator SPECTER. We will give you all the time you need, Dr. Varmus.

Dr. VARMUS. Thank you. I am very pleased to have a chance to join you at this hearing to discuss mainly the recently published work by Dr. Jamie Thomson and Dr. John Gearhart that has excited both the scientific community and the public. What these scientists have done is to establish lines of pluripotent human stem cells, cells that grow continuously in culture and are capable of forming many different kinds of tissues. This work does warrant public attention because of its scientific and medical promise and because of the ethical concerns that it raises.

I briefly would like to consider five questions. First, what are stem cells, especially pluripotent stem cells? Second, what are the potential uses of these stem cells? Third, what methods have been used to make pluripotent stem cells? What is the ethical status of pluripotent stem cells? And finally and briefly, what is the role of NIH in these endeavors?

I am going to use some charts, Senator, to try to make things clear.

[Chart.]

Let me begin by pointing out that there are many different kinds of stem cells. Stem cells have the general properties of being able to renew themselves, as indicated by these arrows, to commit themselves to a higher degree of differentiation, a higher, more specialized function, and to undergo this level of commitment with time. Shortly after fertilization——

Senator SPECTER. Dr. Varmus, would you pull one of those microphones over to you a little more closely. Thank you.

Dr. VARMUS. Early in the process of the development of a human being, after fertilization, cells are completely potent, able to develop to give rise to a complete organism. Those cells are called totipotent.

With time, cells become more highly specialized, resulting in the formation of cells we call pluripotent, able to make many different kinds of cells, but not give rise to an entire organism.

Over the course of development, cells become yet more specialized and develop into stem cells that are committed to certain specific tissue lineages, like blood or muscle or liver or nerve. Such stem cells, that can give rise to specific tissues and are committed to those lineages, are found both in the course of development in the fetus and in adults, and you're no doubt familiar. For example, so-called blood or hematopoietic stem cells were recently in the news as a result of recent publications indicating that such stem cells can be isolated, for example, from cord or placental blood and used as a source of treatment in patients who are undergoing bone marrow transplantation for cancer.

Indeed, there is a great deal of research going on with these mature forms of stem cells that are committed to specific lineages, and much of that research, supported by the NIH and by industry, has achieved therapeutic status in the case of bone marrow stem cells or blood stem cells, and much work is going on with experimental animals to develop other kinds of stem cells for various kinds of uses.

[Chart.]

But what are the great uses to which these so-called pluripotent stem cells might be put? There are a variety of venues for such research. First of all, since these cells are relatively primitive in their place in the hierarchy, they can be used to study the differentiation process that gives rise to many different kinds of tissues, and this is going to hopefully allow us to understand the origin of birth defects and to understand many abnormalities of cell behavior, such as occur in cancer, for example.

That, of course, goes on at the fundamental level. These cells may also have many applied uses, for example in identifying targets for development of new pharmaceuticals or for carrying out simple means to assess the toxicity of candidate pharmaceuticals.

In the realm of therapy, such stem cell lines that are pluripotent in character may well be useful for developing therapies that supply missing or defective tissues in a wide variety of diseases—cells for patients with diabetes, heart muscle cells for patients who have impaired cardiac function, nerve cells for patients with a variety of neurodegenerative diseases, like Parkinson's or Alzheimer's, and, of course, bone marrow precursors for patients who have disorders of the blood-forming system or have been treated for cancers.

Now, the assumption that all this work can be done is based upon the fundamental research necessary to learn how to efficiently differentiate pluripotent cells into the respective lineages and to overcome the traditional problem of tissue rejection due to the immune system.

How do we get to the point of obtaining such pluripotent cells? [Chart.]

Now, there are many ways that this can be done, but let me focus on the two that will be the subject of discussions by Doctors Gearhart and Thomson. I should mention that these methods were developed with NIH funds to study how cells develop in experimental animals, particularly the mouse.

Let me first remind you about the normal sequence of events in a simple manner. Development begins, of course, with fertilization of an egg by a sperm, shown here as occurs in a test tube. That cell undergoes a series of divisions, still producing cells that are fully capable of giving rise to an embryo. But those cells go through further divisions and undergo the first round of specialization, producing this sac-like structure called a blastocyst, in which the cells that will give rise to the mature individual are referred to as cells within the inner cell mass.

The blastocyst then undergoes implantation in the womb and eventually may give rise to a fetus, which eventually may give rise to a newborn infant.

In the work conducted by Dr. Thomson, cells were taken from the inner cell mass and placed into a petri dish under defined conditions that he will describe for you and were then grown in culture, producing what are referred to as pluripotent cells and proved to be so by a variety of criteria.

In Dr. Gearhart's work, cells were taken from the gonadal region of a fetus which was obtained from a terminated pregnancy. These cells from the gonadal region, so-called primordial germ cells, were cultured under specialized conditions and proven by a variety of

tests to be capable of giving rise to a variety of tissues—hence this cell line was also called pluripotent.

[Chart.]

Let me say a few words about the status of such cells. There are many issues to be raised about the cells that we're talking about today, but one of those questions is whether these cells have the ability to give rise to a complete human being. The answer to that from a scientific perspective is no.

I remind you that cells that are developed by fertilization, cells early in development, or intact blastocysts can, when reintroduced into a womb, give rise to an infant, whereas cells removed from the inner cell mass or grown as cultured pluripotent stem cells if reintroduced into a uterus do not give rise to a new human being. Hence, these pluripotent cells cannot be considered organisms and cannot be considered to be embryos.

Now, let me turn at this point to a few additional considerations. Despite what I have just told you about the fact that pluripotent stem cells are not organisms and are not embryos, because pluripotent stem cells are derived from human organisms early in their development, the use of these cells has raised legitimate public concerns and the cells do deserve special ethical consideration.

As you will hear from the final panel of witnesses, there is a wide range of views about the moral status of these cells and the developmental states from which they are derived. These views must, in my opinion, be taken into consideration in doing research with such cells.

For example, in 1994 the NIH issued a report from its panel on human embryo research that carefully reviewed the medical benefits and the ethical quandaries that are presented by these and other types of experiments. Then, 2 weeks ago President Clinton asked the National Bioethics Advisory Commission to give him further advice in the wake of recent publications.

Finally and briefly, what is the role of NIH in these endeavors? Federal funds were not used in the experimental work that you will hear about from Doctors Gearhart and Thomson concerning human cells. The funding of Dr. Thomson's work by the NIH was indeed forbidden by an amendment to our appropriation bill. He used embryos that were remaining in an in vitro fertilization clinic, donated by parents who had successfully achieved pregnancy in a treatment for infertility. Funding of Dr. Gearhart's work by the NIH would have been possible under existing law, but he obtained support from private industry instead.

Now, I cannot overemphasize that we at the NIH see enormous promise in the work that is being discussed here today. We also believe that it is beneficial, in general, for medical research to be conducted in the public domain, with open dialog, with careful oversight, and with maximum opportunity for participation by the best minds in our country.

But, we also respect existing laws. We recognize the need for public education about these complex issues, such as is occurring today, and we insist on clear guidelines and careful oversight for any research that might be carried out with these cell lines or other controversial materials under Federal law.

PREPARED STATEMENT

Again, I thank you, Senator, for having the subcommittee provide a venue for this important discussion, and I will be very pleased to answer any questions that you might have.

Senator SPECTER. Thank you very much, Dr. Varmus. We have turned off the red light to allow you to describe in somewhat greater detail the specifics here.

[The statement follows:]

PREPARED STATEMENT OF HAROLD VARMUS M.D.

Mr. Chairman and Members of the Subcommittee, I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before you to discuss recent published reports on the isolation and propagation of the first human pluripotent stem cell lines. These findings, reported by Drs. John Gearhart from Johns Hopkins University and James Thomson from the University of Wisconsin, bring medical research to the edge of a new frontier that is extraordinarily promising. The development of human pluripotent stem cell lines deserves close scientific examination, further evaluation of the promise of the research, and careful consideration and open discussion of the ethical and legal issues. I want to thank you for the opportunity to discuss this important issue with you and the Members of this Subcommittee.

Why the excitement? For the first time, scientists have obtained human stem cells that can give rise to many types of cells in our body. Let me briefly describe these experiments. Dr. Thomson and coworkers derived stem cell lines from embryos donated by couples undergoing in vitro fertilization (IVF) as part of treatment for infertility. These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue typesendoderm (which goes on to form the lining of the gut), mesoderm (which gives rise to muscle, bone and blood) and ectoderm (which gives rise to epidermal tissues and the nervous system). The ability of the cells to specialize into the three major tissues types is an important indicator that these cells are pluripotent. Dr. Gearhart and his coworkers derived pluripotent stem cells from fetal gonadal tissue destined to form germ cells. When grown in culture, these cells resemble other types of pluripotent stem cells in that they, like the cells from Dr. Thomson's work, also can develop into cells of the three major tissue types.

WHAT ARE STEM CELLS?

As policy makers proceed to consider the scientific, ethical and societal issues raised by this research, it is absolutely essential to clarify terms and definitions. There are many types of stem cells. In general, they all have the ability to divide (and self renew) and to commit to a more specialized function. There is a hierarchy of stem cell types. Some stem cells are more committed than others. Some stems cells—the pluripotent stem cell we are discussing today—have the ability to become many, but not all, of the cells types in the human body.

Through processes we are only beginning to understand, primitive stem cells can be stimulated to become specialized, so that they are precursors to any one of many different cell types such as muscle cells, skin cells, nerve cells, liver cells. Unlike the stem cells from which they are derived, these specialized cells are "committed" to a particular function.

All stem cells have the capability of self-renewal, i.e., they can continually reproduce themselves. Cells from the very earliest embryo (up to about the 16 cell stage) are totipotent stem cells. They are "totally potent" or totally capable of forming all cells of the body, including the cells required to support embryonic and fetal development. Each cell of this early embryo has the potential to develop into a human being.

After a few days of development, the early embryo forms a hollow ball of cells, called a blastocyst. This is the next stage of embryonic development. The clustered cells within this ball are called the inner cell mass. The cells in the inner cell mass are not totipotent. Rather, they are pluripotent. Pluripotent stem cells are more "committed" than totipotent stem cells. Unlike the fertilized egg, or the early embryo, or the intact blastocyst, neither the disaggregated inner cell mass nor the pluripotent stem cells derived from it (nor the pluripotent stem cells derived from fetal germ cells) will produce a human being even if returned to a woman's uterus. These cells do not have the potential to form a human being, because they do not

have the capacity to give rise to the cells of the placenta or other extraembryonic tissues necessary for implantation, nor can they support fetal development in the uterus.

During fetal development, pluripotent stem cells become even more committed, i.e, they have the capacity to form only one or a few different kinds of cells. For example, hematopoietic stem cells can form all the blood cells, but no other tissue types. The adult human being continues to harbor many types of stem cells responsible for the body's ability to repair some but not all tissues. Stem cells that permit new skin growth and renewal of blood cells are two examples.

POTENTIAL APPLICATIONS OF PLURIPOTENT STEM CELLS

There are several important reasons why the isolation of human pluripotent stem cells is, indeed, important to science and for the future of public health. At the most fundamental level, pluripotent stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the most basic kind of research—the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses.

Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body. Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue. Unfortunately, the number of people suffering from these disorders far outstrips the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation. Let me expand on two of these examples.

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

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

While I have taken this opportunity to outline the promise of this research, there is much to be done before we can realize these innovations. First, we must do the basic research to understand the cellular events that lead to cell specialization in the human, so that we can direct these pluripotent stem cells to become the type(s) of tissue needed for transplantation in great numbers. And before we can use these cells for transplantation, we must overcome the well-known problem of immune rejection. Because human pluripotent stem cells derived from embryos or fetal tissue would likely be genetically different from the recipient, future research would need to focus on modifying human pluripotent stem cells to minimize tissue incompatibility. Technological challenges remain before these discoveries can be incorporated into clinical practice. These challenges, though significant, are not insurmountable.

HOW ARE PLURIPOTENT STEM CELLS PRODUCED?

There are several ways to produce human pluripotent stem cells. These methods have been developed over the past 17 years by researchers working with animals. The work you will hear about today builds on this important basic animal research.

As I mentioned earlier, one method of creating these pluripotent stem cells was described by Dr. Thomson and his coworkers. The techniques they used were initially developed using mice. Dr. Thomson first made stem cells from non-human primates. In the most recent work, they used inner cell mass cells from blastocyst stage human embryos that were created in the course of infertility treatment and donated by couples for research to derive stem cells. The researchers allowed cell division to continue in culture to the blastocyst stage and then removed the inner cell mass, which was cultured to derive pluripotent stem cells.

Pluripotent stem cells can also be derived from fetal tissue, as was first done using primordial germ cells from mouse fetal tissue. Dr. Gearhart and coworkers isolated human primordial germ cells, the cells that will go on to become eggs and sperm, from 5–9 week old fetal tissue obtained after pregnancy termination. When grown in culture, these stem cells appear to be pluripotent.

It may also be possible to make human pluripotent stem cells by using somatic cell nuclear transfer—the technology that received so much attention with the announcement of the birth of the sheep, Dolly. Although there has been no scientific publication of this to date, presumably any cell from the human body (except the egg or sperm cell) could be fused with an enucleated egg cell and stimulated to return to highly immature, pluripotent and possibly totipotent state.

THE ROLE OF THE FEDERAL GOVERNMENT

Federal funds were not used in either of the experiments that you will hear about today. First, let me first address Dr. Thomson's work in which cells were derived from embryos created by in vitro fertilization but not used for infertility treatment. This work falls clearly within the Congressional ban on human embryo research. NIH could not, and did not, support Dr. Thomson's recent work developing this cell line. The same restrictions do not apply to Dr. Gearhart's work, although it may be governed by other laws and regulations. Dr. Gearhart derived his pluripotent stem cells from fetal tissue from terminated pregnancies. The Public Health Service Act authorizes Federal funding of human fetal tissue research and provides safeguards for its conduct. The department may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes if a number of statutory requirements are met. Thus, if Dr. Gearhart's research falls within these boundaries, NIH could have supported his recent work deriving pluripotent stem cells from fetal tissue, as long as he followed these Federal statutes and regulations. For the record, NIH did not, however, support any of this research.

ETHICAL ISSUES

I have just described the science and the medical promise of research on the pluripotent stem cell. But the realization of this promise is also dependent on a full and open examination of the social and ethical implications of this work. The fact that these stem cells were produced from embryos and fetal tissue raises a number of ethical concerns including, for example, the need to ensure that stem cell research not encourage the creation of embryos or the termination of pregnancies for research purposes. In strict accordance with the President's 1994 directive, no NIH funds will be used for the creation of human embryos for research purposes. We also will continue to abide by relevant statutes.

The ethical and social issues associated with stem cell research are complex and controversial and require thoughtful discourse in public fora to reach resolution. To this end, the President has asked the National Bioethics Advisory Commission to undertake a thorough review of the issues associated with human stem cell research, balancing all ethical and medical considerations.

SUMMARY

The development of cell lines that may produce almost every tissue of the human body is an unprecedented scientific breakthrough. It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life.

Mr. Chairman, I am grateful to you for providing a forum to present information about this promising arena of science and medicine. I would be pleased to answer any questions you might have.

NONDEPARTMENTAL WITNESSES

STATEMENT OF JOHN D. GEARHART, Ph.D., PROFESSOR OF GYNECOLOGY AND OBSTETRICS, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Senator SPECTER. I think it would be useful—we have a very long list of witnesses—if we invited at this time the next three witnesses to join the panel because we will be talking about very similar subjects, and then we will return to the question and answer session. So let me call now for Dr. John Gearhart, Dr. James Thomson, and Dr. Michael West to join us at the panel.

Our first witness is Dr. John Gearhart, a professor of gynecology and obstetrics at Johns Hopkins University. Dr. Gearhart received his undergraduate degree from Penn State and his Ph.D., from Cornell University in genetics, and has some very fascinating results to report to us here this morning.

So we will begin with you, Dr. Gearhart. We would like to observe the 5-minute time limit, leaving the maximum amount of time for questions and answers. Thank you for joining us and the floor is yours.

Dr. GEARHART. Thank you for the opportunity to appear before the committee and to provide the committee with insight into the research in which we have been engaged for the last 5 years. I feel strongly that the medical benefits of this research will be enormous and that we are excited about its potential.

Dr. Varmus has covered the salient features of embryonic or pluripotent stem cells. I would like to reinforce a few points and then I would like to tell you how we performed our experiments.

The most important point I think to be reinforced is the fact that, although these cells can form many different cell types, they are unable by themselves to form an embryo or a human being.

A bit of perspective. For the past 20 years I have been involved in Down Syndrome research. This research has been sponsored through the National Institutes of Health, and one of the conclusions from our studies of 20 years is that many of the events that lead to the abnormalities that one sees in Down Syndrome occur very early during pregnancy, very early in embryogenesis, at stages that we cannot have access to.

In studies from the mouse using embryonic stem cells, we are able to look at very early developmental events utilizing these cells, and thus our desire to establish human cells with which we can study aspects of early development, focusing on Down Syndrome.

[Chart.]

The procedure that we used in the laboratory is depicted on the first placard. We obtained from autopsy material, fetal autopsy material, this structure here—I hope I do not blind somebody—which is a very small piece of tissue in which the primordial germ cells reside from the period of 5 to 7 weeks post-fertilization. This piece

of tissue is dissociated, placed in culture under certain conditions such that these cells will grow, the germ cells, and will convert, for lack of a scientific term, into a pluripotential stem cell.

I want to emphasize that this technology was first developed in the mouse and we adapted it to the human. We did not have to work it out in the human per se, just adapt it.

These cells, as depicted in our publication, have many of the properties of embryonic stem cells. Our studies have followed Federal, that is FDA and NIH, guidelines, State guidelines, and institutional guidelines. Our research has been rigorously reviewed annually by the Johns Hopkins School of Medicine institutional review board, which considers not only scientific merit but also ethical considerations of the work.

What of the application of this work? Well, we have mentioned several times here its use in tissue transplantation, birth defects studies, et cetera. My main interest coming into this has been in aspects of birth defects, and directed primarily to Down Syndrome.

[Chart.]

I would like to show you on the next placard, though, some more recent results. What is depicted here are images of mature human neurons that have been grown from embryonic stem cells in culture. Embryonic stem cells have been grown for a period of 3 months and then treated over a period of 5 days so as to encourage these cultures to form neurons. They are human, they have the features of neurons, and this would go to show, I think, some of the power of this technology from the standpoint of being able to derive these different tissues in culture which could perhaps then be used for tissue transplantation studies.

PREPARED STATEMENT

In conclusion, I firmly believe that this research holds the potential for treatments of catastrophic and debilitating diseases and injuries that affect millions of Americans. What is needed to realize this potential as soon as possible is Federal support and oversight such as that that the NIH could provide and that the investigators in this area not be restricted in their endeavors, so that we may bring the products of this technology to the patients as soon as possible.

Thank you, Mr. Chairman.

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

[The statement follows:]

PREPARED STATEMENT OF JOHN GEARHART

My name is John Gearhart and I am a Professor of Gynecology and Obstetrics at the Johns Hopkins University School of Medicine. My research interests are in how genes regulate the formation of tissues and embryos. For the past 18 years my research has focused on Down Syndrome in attempts to determine the causes of the birth defects characteristic of this syndrome, with special emphasis on mental retardation. As a result of our studies, it is apparent that the events leading to the many birth defects characteristic of the syndrome occur in the very early stages of the embryo's development, at stages not accessible for study. Because of this limitation, I sought to develop another approach that would enable us to study theses key events. The approach I sought was to use human pluripotential stem cells (hPSC). HPSCs will enable us to study the formation of specific tissues that would reveal the cellular mechanisms resulting in the pathogenesis found in Down Syndrome. Knowing how and when abnormalities arise will enable us to design therapies to

ameliorate the devastating effects of developmental disabilities and enable individuals to have a better quality of life.

In order to use human stem cells in the study of birth defects, the first step was to culture hPSCs in the laboratory, something that had not been done before we began our attempts in 1993. Over several years I was able to put together a research team consisting of Drs. Michael Shamblott, Peter Donovan, John Littlefield, Paul Blumenthal, and George Huggins, with the excellent technical support of Elizabeth Bugg and Joyce Axelman. This past year, Shunping Wang, a graduate student, joined the team. On November 10th of this year we reported in the Proceedings of the National Academy of Sciences our results on the culturing of cells with properties of hPSCs. A copy of that paper is submitted with this testimony.

I would like to place our recent work on hPSCs in perspective. hPSCs are unique cells in that they have both the capacity to form any of the over 200 different cell type in the body and to self-renew the stem cell population. These properties can be realized in the laboratory, that is, the stem cells can be grown indefinitely in tissue cultures dishes and, under appropriate culture conditions, they will form other cell types. It is important to note that while these cells have the capacity to form a variety of cell types, they cannot form embryos. Our laboratory used primordial germ cells (PGCs) as starting material to derive the stem cells. PGCs are cells whose descendants are sperm and eggs. PGCs were collected from autopsy material of therapeutic pregnancy terminations and placed in tissue culture. Over a period of two weeks in culture the PGCs develop into pluripotential stem cells.

It has been well documented from animal studies that PSCs have full developmental potential. Both in animals and in the culture dish, these cells can form a wide variety of cell types including blood cells, blood vessels, skeletal and cardiac muscle, and nerve tissue have been shown to develop from these cells in the laboratory. I have presented examples here today of nerve cells produced in the laboratory from the human stem cells.

Although we can demonstrate a variety of cell types formed in the laboratory from these cells, we do not yet know how to control which cell types will form. This is one of the next challenges, to determine how to direct all the stem cells in the culture dish to form specific cell types, such as pancreatic islet cells, cholinergic neurons, dopaminergic neurons, cardiac muscle, lymphocytes, etc. These cell types are at risk in some of our more devastating diseases and a tissue culture source would be ideal for therapies that are mentioned below. The time frame for accomplishing this phase of the research will be directly correlated to the research efforts of laboratories involved in this research effort. Only a supportive research environment, both in terms of policy and resources, will move this work forward rapidly.

What is to be gained from studies using hPSCs? I mentioned that my group's initial motivation in attempting to isolate a human pluripotent line was to provide a powerful tool for determining the bases of the abnormalities seen in Down Syndrome, something we have been studying for two decades. We have learned that the bases for many of the features of this syndrome are initiated very early in the embryo. Without a human pluripotential cell line, it would be impossible to study the cells and tissue in which these features are initiated. However, with this tool scientists may better understand mechanisms behind the formation, and malformation, of distinct tissue types. With this understanding, biomedical science may someday be able to alleviate the worst of these features, such as mental retardation, in Down Syndrome as well as other genetically based developmental abnormalities. Without question, hPSCs will have the greatest impact on medicine through their utilization in tissue transplantation therapies in which tissues or cells are engrafted into organs, which have been destroyed through disease or injury. Tissue transplantation therapy has become increasingly important in the last two decades. Traditional tissue transplantation therapies utilize such tissues as bone marrow, bone, skin, etc. However, as each day passes, new therapies are envisioned which tax current donation protocols. An example of such a novel therapy is the use of tissue transplantation for the treatment of Parkinson's Disease. This therapy began with the transplantation of the patient's own dopaminergic adrenal medullary tissue into the degenerating portions of the brain. The next development in the treatment of Parkinson's was the utilization of fetal neural tissue instead of adrenal tissue. The fetal tissue, due to its more plastic state and its ability to grow and integrate into the host environment, offers an effective treatment of Parkinson's disease.

With the rise of these novel tissue transplantation therapies, equally novel graft resources have been sought. These include adult-derived stem cells, such as those found in muscle; genetically engineered graft tissue, non-human animal tissue, human fetal tissue and, finally, the use of hPSCs. Eventually, through our abilities to control what cell types are formed from the stem cells in the laboratory and through the optimization of transplantation protocols, the hPSCs will enable a pan-

oply of new treatments. Along with Parkinson's disease, it is likely that the symptoms of other neurodegenerative disorders and injuries, such as Alzheimer's disease, Huntington disease, stroke and spinal cord injury could be effectively ameliorated and quality of life improved. Neurodegenerative disorders are by no means the only conditions to which the use of human pluripotent stem cells could apply. The bankable pluripotential stem cells could be induced to form insulin-producing pancreatic b-cells to make diabetics less dependent on insulin injection. Muscle stem cells could also conceivably be produced from human pluripotential stem cells in a large enough yield to help those with muscular dystrophies regain better motor control. Cardiac muscle stem cell could be derived and subsequently used to help in the treatment of degenerative heart disease and perhaps decrease the necessity of more complicated and more costly whole organ transplantation.

One of the major limitations of tissue transplantation is the issue of graft rejection. The patient's immune system must be compromised to allow for the presence of the graft. This generally involves the use of powerful drugs with side affects. In animal studies, it has been found that stem cells can be genetically manipulated so as to modify graft rejection. It may eventually be possible to produce universal donor cell lines in the laboratory through the use of hPSCs.

The capability of hPSCs to form a variety of cell types, their ability to self-renew in the laboratory (and to be banked) and their ability to be genetically manipulated to enhance their transplantation efficiency, all support the contention that these cells will be an invaluable resource in transplantation medicine.

Our research has been reviewed and approved annually by the Institutional Review Board of the Johns Hopkins University School of Medicine whose composition includes ethicists, religious leaders, lay people, and doctors. This committee insures that we are in compliance with all Federal, State and institutional requirements, from patient consent, to record keeping, to safety. This committee considers ethical issues as well as the scientific merit and research protocols. Our research on stem cells has been supported through endowment funds to my division in Gynecology and Obstetrics until last year, when we received funding from Geron Corporation of Menlo Park, CA. My involvement with Geron Corporation has been reviewed and approved by the Conflict-of-Interest Committee for the Johns Hopkins University School of Medicine.

In conclusion, research with pluripotent human stem cells holds enormous promise for treatments of catastrophic and debilitating diseases and injuries affecting millions of Americans. To realize the full medical potential of these cells, it is imperative that this work goes forward in a supportive research environment with appropriate overview and regulation. It is my opinion that this work should be eligible for Federal funds and that the National Institutes of Health should be given the responsibility to develop policy and guidelines, review research applications, and award research grants on human pluripotential stem cells. Only through the mechanism of NIH oversight and support will the American people be assured that the medical benefits of these cells for alleviating suffering will progress as rapidly as possible and that any concerns that they may have will be taken into account.

Thank you for the opportunity to address the committee on this important issue.

This statement was prepared with the assistance of Brian Edwards.

STATEMENT OF JAMES THOMSON, Ph.D., ASSOCIATE RESEARCH ANIMAL VETERINARIAN, WISCONSIN REGIONAL PRIMATE RESEARCH CENTER

Senator SPECTER. We turn now to Dr. James Thomson, Associate Research Animal Veterinarian at the Wisconsin Regional Primate Research Center, a graduate of the University of Pennsylvania in veterinary medicine, a Ph.D. in molecular biology, author of numerous scientific publications in his field.

Thank you for joining us, Dr. Thomson. The floor is yours.

Dr. THOMSON. I would like to thank the committee for inviting me. What I have to say overlaps a great deal with what Dr. Varmus and Dr. Gearhart said, so I will be fairly brief.

My group has recently reported the derivation of human embryonic stem cell lines. As you have heard, these are undifferentiated cells. This means that they do not look like the cells that make up the adult body. They are not yet committed to become specific things. These undifferentiated cells——

Senator SPECTER. People are straining to hear you in the audience, so would you put the microphone closer, please.

Dr. THOMSON. These undifferentiated cells can proliferate in tissue culture indefinitely. That means we can make as many of these cells as we want to and we know no biological limit to the numbers of these cells we can make.

What is important about these cells is that, even after prolonged culture for months and potentially years, they maintain the ability to form many, if not all, of the cells that make up the adult body.

Now, our cells differ in their source, where they came from, compared to Dr. Gearhart's. Our cells were derived from the pre-implantation embryo. They were derived from in vitro-fertilized produced embryos, and these were produced for clinical purposes, but they are in excess of the clinical needs of the couples and the couples donated them specifically for this project instead of actually discarding them. The informed consent process was detailed and specified the purpose of the research, its context, and its implications.

Now, as you have heard, human embryonic stem cells are important because they could provide large purified populations of human cells, such as muscle cells, pancreatic cells, or neurons for transplantation therapies. Many diseases, including diseases such as juvenile onset diabetes and Parkinson's disease, result from the death or dysfunction of just one or a few cell types, and the replacement of those cell types can potentially offer life-long treatments.

These cells are also important because they will offer insights in development events that cannot be studied directly in the intact human embryo, but which have important consequences in clinical areas, including birth defects and fertility and pregnancy loss, and John Gearhart touched on Down Syndrome, for example.

Screening tests that use specific ESL derivatives will allow the identification of new drugs, the identification of genes that could be used for tissue regeneration therapies, and the identification of toxic compounds.

Although the long-term potential for human therapies resulting from human ESL cell-line research is enormous, these therapies will take years to develop. Significant advances in developmental biology and transplantation medicine are required, but I believe that therapies resulting from human ESL research will become available within my lifetime.

How soon such therapies will be developed will depend on whether there is public support of research in this area. Private companies will have an important role in bringing new ESL-related therapeutics to the marketplace. However, the current ban in the United States on the use of NIH funding for human embryo research discourages the majority of the best U.S. researchers from advancing this promising area of medical research.

Human pre-implantation embryo research was reviewed in depth by the NIH human embryo research panel 1994. The NIH panel recognized the therapeutic promise of human embryo research, while recognizing that the human embryo warrants serious moral considerations as a developing form of human life. For these reasons the panel concluded in part:

FEDERAL FUNDING AND REGULATION

It is in the public interest that the availability of Federal funding and regulation should provide consistent ethical and scientific review for this area of research. The panel believes that, because the pre-implantation embryo possesses qualities requiring moral respect, research involving the ex utero pre-implantation embryo must be carefully regulated and consistently monitored.

I agree with these conclusions.

PREPARED STATEMENT

This hearing on embryonic stem cell research is timely and I hope that I can help you better understand the work we have done and its medical and ethical implications. I would be pleased to answer any of your questions.

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

[The statement follows:]

PREPARED STATEMENT OF JAMES A. THOMSON

OVERVIEW

My name is James Thomson and I'm a developmental biologist at the University of Wisconsin-Madison. My group has recently reported the derivation of human Embryonic Stem (ES) cells that can proliferate indefinitely in tissue culture and yet maintain the potential to form many, and possibly all, adult cell types. Human ES cells thus provide a potentially unlimited source of specific differentiated cell types for basic biological research, pharmaceutical development, and transplantation therapies. These human ES cell lines were derived from in vitro fertilized embryos before the formation of any fetal structures. These embryos were produced by in vitro fertilization for clinical purposes, but were in excess of clinical needs and were donated after informed consent. The informed consent process was detailed and specified the purposed of the research, its context, and its implications.

Human ES cell lines are important because they could provide large, purified populations of human cells such as heart muscle cells, pancreatic cells, or neurons for transplantation therapies. Many diseases, such as juvenile onset diabetes mellitus and Parkinson's disease, result from the death or dysfunction of just one or a few cell types, and the replacement of those cells by transplantation could offer lifelong treatment. Human ES cells are also important because they will offer insights into developmental events that cannot be studied directly in the intact human embryo, but which have important consequences in clinical areas, including birth defects, infertility, and pregnancy loss. Screening tests that use specific ES cell derivatives will allow the identification of new drugs, the identification of genes that could be used for tissue regeneration therapies, and the identification of toxic compounds.

Although the long-term potential for human therapies resulting from human ES cell line research is enormous, these therapies will take years to develop. Significant advances in developmental biology and transplantation medicine are required, but I believe that therapies resulting from human ES cell research will become available within my lifetime. How soon such therapies will be developed will depend on whether there is public support of research in this area. Private companies will have an important role in bringing new ES cell-related therapeutics to the marketplace; however, the current ban in the U.S. on the use of Federal funding for human embryo research discourages the majority of the best U.S. researchers from advancing this promising area of medical research. Human preimplantation embryo research was reviewed in depth by the National Institutes of Health (NIH) Human Embryo Research Panel in 1994. The NIH Panel recognized the therapeutic promise of human embryo research while recognizing that the human embryo warrants serious moral consideration as a developing form of human life. For these reasons, the panel concluded in part, "It is in the public interest that the availability of Federal funding and regulation should provide consistent ethical and scientific review for this area of research. The Panel believes that because the preimplantation embryo possesses qualities requiring moral respect, research involving the ex utero preimplantation human embryo must be carefully regulated and consistently monitored." I agree with these conclusions. This hearing on embryonic stem cell line research is timely. I hope I can help you better understand the work we have done and its medical and ethical implications, and I would be pleased to answer any questions that you have.

WHAT ARE HUMAN EMBRYONIC STEM CELLS?

In the adult mammal, cells with a high turnover rate are replaced in a highly regulated process of proliferation, differentiation, and programmed cell death from undifferentiated adult "stem cells". Tissues from which stem cells have been extensively studied include blood, skin, and the intestine. In the human small intestine for example, approximately one hundred billion cells are shed and must be replaced daily. Although various definitions have been proposed, characteristics of adult stem cells generally include: (i) prolonged proliferation, (ii) self-maintenance, (iii) generation of large numbers of progeny with the principle phenotypes of the tissue, (iv) maintenance of developmental potential over time, and (v) the generation of new cells in response to injury. Thus, stem cells in the adult sustain a relatively constant number of cells and cell types. Several properties of adult stem cells limit their therapeutic potential. First, all adult stem cells are committed to becoming a relatively restricted number of cell types. Second, although adult stem cells can divide for prolonged periods, cell division can occur only a finite number of times, so there is a limit to how much they can be expanded in tissue culture. Third, the sustainable culture of adult stem cells has not yet been achieved. And fourth, several tissues of clinical importance, such as the heart, completely lack stem cells in the adult. Thus, after a heart attack, when heart muscle dies, there is no regeneration of heart muscle, only the formation of non-functional scar tissue.

In contrast to the adult, embryonic cell proliferation and differentiation elaborates an increasing number of cells and cell types. In mammals, each cell of the cleavage stage embryo has the developmental potential to contribute to any embryonic or extraembryonic cell type, but by the blastocyst stage, cells on the outside of the embryo (the trophectoderm) are committed to a particular cell type found in the placenta (Figure 1). The cells on the inside of the blastocyst (the inner cell mass) contribute to all the tissues of the embryo proper. Soon after the blastocyst stage, cells of the inner cell mass develop into cells that are developmentally restricted to particular lineages. Because the cells of the inner cell mass proliferate and replace themselves in the intact embryo for a very limited time before they become committed to specific lineages, they do not satisfy the criteria for stem cells that are applied to adult tissues. In contrast, if the inner cell mass is removed from the normal embryonic environment and dissociated under appropriate conditions, the cells will remain undifferentiated, replace themselves indefinitely, and maintain the developmental potential to contribute to all adult cell types. Thus, these inner cell mass-derived cells satisfy the criteria for stem cells outlined above, and they are referred to as embryonic stem (ES) cells. The derivation of mouse ES cells was first reported in 1981. We have recently described the isolation of human ES cell lines that satisfy the following criteria for ES cells: (i) derivation from the pre- or peri-implantation embryo, (ii) prolonged undifferentiated proliferation, and (iii) stable developmental potential after prolonged culture to form differentiated derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm) which are the three basic lineages that give rise to all of the cells of the adult. Cells we have already observed to differentiate from human ES cell lines have included gut epithelium (endoderm), cartilage, bone, and smooth and striated muscle (mesoderm); and neural epithelium, embryonic ganglia, and stratified squamous epithelium (ectoderm).

WHY ARE HUMAN ES CELLS IMPORTANT?

Human ES cell lines could offer insights into developmental events that cannot be studied directly in the intact human embryo or in other species, but which have important consequences in clinical areas, including birth defects, infertility, and pregnancy loss. Particularly in the early post-implantation period, knowledge of normal human development is largely restricted to the description of a limited number of sectioned embryos and to analogies drawn from the experimental embryology of other species. Although the mouse is the mainstay of experimental mammalian embryology, early structures including the placenta, extraembryonic membranes, and the egg cylinder all differ significantly from those of the human embryo. Human ES cell lines will be particularly valuable for the study of the development and function of tissues that differ between mice and humans.

Elucidating the mechanisms that control differentiation will facilitate the directed differentiation of ES cells to specific cell types. The standardized production of large, purified populations of normal human cells such as heart muscle cells and neurons will provide a potentially limitless source of cells for drug discovery and transplantation therapies. For example, large purified populations of ES cell-derived heart muscle cells could be used to find new drugs to treat heart disease. Many diseases, such as Parkinson's disease and juvenile onset diabetes mellitus, result from the

death or dysfunction of just one or a few cell types. The replacement of those cells could offer lifelong treatment. In addition to Parkinson's disease and juvenile onset diabetes, the list of diseases potentially treated by this approach is long, and includes myocardial infarction (heart muscle cells and blood vessels) atherosclerosis (blood vessels) leukemia (bone marrow), stroke (neurons), burns (skin) and osteoarthritis (cartilage). For the foreseeable future, these therapies will involve the repair of organs by the transplantation of cells or simple tissues, but not the replacement of entire organs.

Strategies to prevent immune rejection of the transplanted cells need to be developed, but could include banking ES cell lines with defined major histocompatibility complex backgrounds or genetically manipulating ES cells to reduce or actively combat immune rejection. Significant advances in basic developmental biology are required to direct ES cells efficiently to lineages of human clinical importance. However, progress has already been made in the in vitro differentiation of mouse ES cells to neurons, hematopoietic cells, and cardiac muscle.

WHY IS THE DERIVATION OF HUMAN ES CELL LINES CONTROVERSIAL?

The derivation of human ES cells lines is controversial both because of the use of human embryos, and because of the properties of ES cell lines. We have derived human ES cell lines from in vitro fertilized embryos at a stage before implantation (the blastocyst stage) and before the formation of any fetal structures. These embryos were produced by in vitro fertilization for clinical purposes, but were in excess of clinical needs. Instead of discarding these embryos, couples donated them specifically for ES cell derivation after informed consent. The use of human embryos generated by in vitro fertilization for any research purpose raises complex ethical issues, and it is beyond the scope of this testimony to review the wide range of views on this subject. Research on human preimplantation embryos has been reviewed in depth by national panels in Britain, Canada, and the United States. In Britain, some research on human preimplantation embryos is allowed, but it is very carefully monitored and regulated, regardless of whether public or private funds are used. The derivation of human ES cell lines is already being publicly funded in Britain. In the U.S., the most recent and complete review of human preimplantation embryo research was completed by the National Institutes of Health (NIH) Human Embryo Research Panel in the fall of 1994. Although the guidelines suggested by the NIH panel do not have the force of law, we followed those guidelines in our derivation of human ES cell lines, as no other Federal guidelines currently exist for privately funded human embryo research. The derivation of human ES cell lines was specifically addressed by the NIH Panel, and it was recommended as acceptable for Federal funding, as long as embryos were not fertilized expressly for that purpose. The subsequent ban on Federal funding for research on human preimplantation embryos has prevented the NIH from funding the derivation of human ES cell lines, and has prevented the NIH from regulating and monitoring research in this area. The NIH Panel both recognized the therapeutic promise of human embryo research and recognized that the human embryo warrants serious moral consideration as a developing form of human life. For these reasons, the panel concluded in part, "It is in the public interest that the availability of Federal funding and regulation should provide consistent ethical and scientific review for this area of research. The Panel believes that because the preimplantation embryo possesses qualities requiring moral respect, research involving the ex utero preimplantation human embryo must be carefully regulated and consistently monitored."

Human ES cell lines are not the equivalent of an intact human embryo. If a clump of ES cells was transferred to a woman's uterus, the ES cells would not implant and would not form a viable fetus. The recent cloning of sheep and mice by the transfer of an adult cell nucleus to an enucleated oocyte demonstrates that at least some adult cells are totipotent (capable of forming an intact embryo that is capable of developing to term). If nuclear transfer from adult cells to enucleated oocytes allows development to term in humans, then the transfer of a nucleus from an ES cell to an enucleated oocyte might also result in a viable embryo. However, if someone wanted to clone a specific famous or infamous individual, the transfer of a nucleus from adult cell would have to be used, not a nucleus from an ES cell. One of the major uses of mouse ES cells has been to genetically modify the germ line (gametes) of mice in very specific ways. However, because of the significant reproductive differences between mice and humans, and the inefficiency of this method of modifying the germ line, human ES cells do not increase the potential for modifying the human germ line. As has already been demonstrated in domestic animal species such as the cow and sheep, nuclear transfer techniques allow a much more efficient way to modify the germ line of species with long generation times.

Thus, if someone wanted to genetically modify the human germ line, there are already other approaches that would be quicker and more efficient than using human ES cells. The NIH Human Embryo Research Panel included recommendations against research involving nuclear transfer to enucleated human oocytes or zygotes followed by transfer to a uterus, and any formation of chimeras with human embryos; these recommendations would effectively preclude the use of ES cells for human cloning or modifying the human germ line.

STATEMENT OF MICHAEL WEST, Ph.D., PRESIDENT AND CHIEF EXECUTIVE OFFICER, ADVANCED CELL TECHNOLOGY

Senator SPECTER. We now turn to Dr. Michael West, president and chief executive officer of the Advanced Cell Technology. Dr. West has a Ph.D., in cell biology from Baylor College of Medicine and has recently noted the use of cloning techniques to create an embryo out of human and cow cells.

We appreciate you joining us, Dr. West, and look forward to your testimony.

Dr. WEST. Thank you, Mr. Chairman, members of the subcommittee. I would like to just expand on a few salient points. You have my written testimony.

First, I think it is important to emphasize what the aims of this research we are discussing today is. The goal is to solve unsolved problems in transplantation medicine. Currently estimates are that upward of half of all health care expenditures in the United States, so that is upwards of $400 billion, can in one way or another be attributed to costs associated with transplantation. Even coronary artery bypass, after all, is a transplantation procedure.

These costs are expected to be aggravated dramatically with the aging of the population. As you know, our population is greying at an alarming rate, such that perhaps up to a sevenfold increase in the number of elderly between 1980 and the year 2030 will occur. So with this is thought to be a dire need for transplantable tissues. You may know that upwards of ten people die every day awaiting a transplantable organ which they do not receive. Many others die for lack of hope of a transplant that could cure their disease. However, their disease could be possibly treated with the technologies we are discussing today.

The problem is two things. First is the availability of tissues. They are simply not available. Many primitive undifferentiated cell types that would be necessary to treat disease like heart failure are not available. The discovery of the human embryonic stem cells and the embryonic germ cell may go a long ways toward supplying the unsupplied demand.

But a second problem is histocompatibility. The cells that Dr. Gearhart and Thomson described have the potential to be genetically engineered to be universal donor cells, so that cells that they derive could potentially be used for all the transplantation of the future. However, there is a distinct risk that that is not a practically achievable goal. We simply do not know today for sure a technology to make these cells universal donor cells. They may indeed, for the foreseeable future at least, require immunosuppressive therapies, drugs that carry with them an inherent risk of rejection, despite immunosuppression and life-threatening complications, including death.

Now, a promising solution which could potentially revolutionize transplantation medicine would be to combine this embryonic stem

cells technology with nuclear transfer technology or cloning technology. Now, the concept here would be that we would take the patient's own cell and fuse it with an egg or oocyte cell that has had its nucleus removed. The belief is that this nuclear transfer procedure can dedifferentiate the cell, taking it back to this primitive state where it can become any cell type, and in addition actually rejuvenates the cell, makes the cell young again. So for elderly patients with degenerative disease this procedure may indeed provide some dramatic improvements in therapy.

The remaining problem, however, is that we simply cannot practically achieve a means of sourcing human oocytes for a large-scale solution to the problems of transplantation. Sourcing human oocytes, we have potentially problematic and cost issues, quality control, and risk to the donor.

So in 1996 Advanced Cell Technology began studies to determine whether we could use an animal oocyte as a means of dedifferentiating a human cell. Now, this is not cloning technology. We are not cloning human beings. The intent is not to clone human beings and we are against the cloning of a human being.

The intent, however, would be to take an animal oocyte and completely remove all genetic information by removing its genomic nucleus that contains all of the DNA and, using that oocyte stripped of its DNA, to reprogram a human somatic cell, then making cells that would be fully compatible with the patient.

PREPARED STATEMENT

This work was done in 1996. In 1997, as you know, there was the announcement of the cloning of Dolly, and on March 4, 1997, President Clinton asked for a voluntary moratorium in the public and private sectors on human cloning. We felt that it would be inappropriate for us to continue this research without further guidelines and backed off from the research. However, we recently announced these preliminary results in the hope of stimulating debate, to hopefully receive guidelines to allow this important technology to move forward. We believe that it would be possible to address one of the most important, significant, and life-threatening problems in medicine today that could be addressed with transplantation.

Thank you.

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

[The statement follows:]

PREPARED STATEMENT OF MICHAEL D. WEST

Mr. Chairman and members of the Subcommittee on Labor, Health and Human Services and Education, my name is Dr. Michael D. West and I am the President and Chief Executive Officer of Advanced Cell Technology a biotechnology company based in Worcester, Massachusetts. A copy of my curriculum vitae is presented in Appendix A.

INTRODUCTION

I am pleased to testify today in regard to the new opportunities and challenges associated with human embryonic stem (ES) cell and nuclear transfer (NT) technologies. By way of introduction, I believe it is important to bring to mind the context of these new opportunities. We are approaching a period in our national history of unparalleled growth of the elderly sector of the population. The aging of the baby boom population along with a general increase in the number of aged people is ex-

pected to increase the number of the elderly sevenfold between 1980 and 2030 A.D. And since the aged use a disproportionately high percentage of healthcare, this "graying of America" is likely to greatly strain our national resources. It has been estimated that transplantation procedures currently account for nearly half of our health care expenditures, approaching $400 billion annually. This is likely to grow even larger with the aging of our population and result in a marked increase in the demand for transplantation. The increased incidence of age-related degenerative disease will likely lead to conflicts of economics, ethics, and aesthetics as we struggle to find a humane and practical means of treating the ailing. Concrete examples of tissues needed will likely include: heart tissue for heart failure, arrhythmias, and ischemic damage, cartilage for arthritis, neurons for Parkinson's disease, kidney cells for kidney failure, liver cells for cirrhosis and hepatitis, skin for burns and ulcers, and bone marrow transplantations for cancer to name only a few. While current procedures are partially successful in alleviating human suffering, these procedures are limited by two major difficulties: (1) the availability of the needed cell or tissue type, and (2) the histocompatibility of the transplanted tissues. As a result, thousands of patients die every year for the lack of transplantable cells and tissues and projections from the Bureau of the Census suggest this shortage will worsen with the aging of our population.

HUMAN ES CELLS

Human ES cell technologies may greatly improve the availability of diverse cell types. Human ES cells are unique in that they stand near the base of the developmental tree. These cells are frequently designated "totipotent" stem cells, meaning that they are potentially capable of forming any cell or tissue type needed in medicine. These differ from previously-isolated stem cells that are "pluripotent" that is, capable of forming several, but only a limited number, of cell types. An example of pluripotent stem cells are the bone marrow stem cells now widely used in the treatment of cancer and other life-threatening diseases.

With appropriate funding of research, we may soon learn to direct these cells to become vehicles of lifesaving potential. We may, for instance, become able to produce neurons for the treatment of Parkinson's disease and spinal cord injury, heart muscle cells for heart failure, cartilage for arthritis and many others as well. This research has great potential to help solve the first problem of tissue availability, but the technologies to direct these cells to become various cell types in adequate quantities remains to be elucidated. Because literally hundreds of cell types are needed, thousands of academic research projects need to be funded, far exceeding the resources of the biotechnology industry.

As promising as ES cell technology may be, it does not solve the second problem of histocompatibility. As shown in Figure 1, human ES cells obtained from embryos derived during in vitro fertilization procedures, or from fetal sources, are essentially cells from another individual (allogeneic). Several approaches can be envisioned to solve the problem of histocompatibility. One approach would be to make vast numbers of human ES cell lines that could be stored in a frozen state. This "library" of cells would then offer varied surface antigens, such that the patient's physician could search through the library for cells that are as close as possible to the patient. But these would likely still require simultaneous immunosuppression that is not always effective. In addition, immunospuppresive therapy carries with it increased cost, and the risk of complications including malignancy and even death.

Another theoretical solution would be to genetically modify the cultured ES cells to make them "universal donor" cells. That is, the cells would have genes added or genes removed that would "mask" the foreign nature of the cells, allowing the patient's immune system to see the cells as "self". While such technologies may be developed in the future, it is also possible that these technologies may carry with them unacceptably high risks of rejection or other complications that would limit their practical utility in clinical practice.

Given the seriousness of the current shortage of transplantable cells and tissues, the FDA has demonstrated a willingness to consider a broad array of options including the sourcing of cells and indeed whole organs from animals (xenografts) although these sources also pose unique problems of histocompatibility. These animal cells do have the advantage that they have the potential to be genetically engineered to approach the status of "universal donor" cells, through genetic engineering. However as described above, no simple procedure to confer such universal donor status is known. Most such procedures are still experimental and would likely continue to require the use of drugs to hold off rejection, drugs that add to health care costs, and carry the risk of life-threatening complications.

THERAPEUTIC CLONING

A promising solution to this remaining problem of histocompatibility would be to create human ES cells genetically identical to the patient. While no ES cells are known to exist in a developed human being and are therefore not available for treatment, such cells could possibly be obtained through the procedure of somatic cell nuclear transfer (NT). In this still largely theoretical procedure, body cells from a patient would be fused with an egg cell that has had its nucleus (including the nuclear DNA) removed. This would theoretically allow the production of a blastocyst-staged embryo genetically identical to the patient that could, in turn, lead to the production of ES cells identical to the patient. In addition, published data suggests that the procedure of NT can "rejuvenate" an aged cell, restoring the proliferative capacity inherent in cells at the beginning of life. Therefore, NT as applied to the production of therapeutic stem cells could have valuable and important applications in the treatment of age-related degenerative diseases.

The use of somatic cell nuclear transfer for the purposes of dedifferentiating a patient's cells for purposes of obtaining undifferentiated stem cells has been designated "Therapeutic Cloning" in the United Kingdom. This terminology is used to differentiate this clinical indication from the use of NT for the cloning of a child which in turn is designated "Reproductive Cloning" in the United Kingdom. In the United Kingdom, the use of NT for therapeutic cloning is being encouraged while legislation has been passed to prohibit reproductive cloning. As promising as NT technologies may be in the arena of therapeutic cloning, a remaining difficulty would be on a source of human oocytes, both for research purposes, but also eventually for large-scale clinical implementation. We believe there may be certain advantages to the use of "surrogate" oocytes from animal sources. Animal oocytes could be supplied in large numbers on an economical basis, they could be "humanized" so as to provide fully human cells with human, rather than animal, mitochondria, and they could also potentially be engineered to be defective in producing a fetus even if used in an inappropriate effort to clone a human being by implantation in a uterus. Since these oocytes would be produced in cloned animals (presumably cows), they could, in principle, offer two advantages: (1) an economical and ethically acceptable source of oocytes for therapeutic cloning, and (2) it is possible that they could be engineered to be effective in dedifferentiating human cells and allowing differentiation into specific lineages, but defective in creating a human embryo if implanted into a uterus. This may prevent the abuse of the technology in the event of an inappropriate use of the technology in attempting to produce a pregnancy.

The NT technologies described above are not designed to be used for the cloning of a human being. Advanced Cell Technology has no intent to clone a human being, and we are opposed to efforts to clone a human being. As of today, we see no clear utility in producing a child by NT, and even if such uses were identified, NT would likely carry with it an inappropriately high risks of embryonic and fetal wastage. However, we believe that the production of genetically-engineered surrogate animal oocytes may be an important resource for medical research, and may solve certain practical and ethical problems associated with sourcing human oocytes and the risks of abuse in human reproductive cloning.

It should be emphasized that the above-mentioned technologies are still in the very earliest stages of development. It is not possible as of today to determine whether the production of human ES cells through sexual or asexual means will meet all the necessary requirements for the development of human therapeutics. What is clear however, is that a careful, informed, and reasoned public discourse would help insure that these technologies could develop to the point where they could be used in the clinic to treat human disease

ETHICAL CONSIDERATIONS

The problem of sourcing human cells and tissues for transplantation raises numerous ethical dilemmas. Because developing embryonic and fetal cells and tissues are "young" and are still in the process of forming mature tissues, there has been considerable interest in obtaining these tissues for use in human medicine. However, the use of aborted embryo or fetal tissue raises numerous issues ranging from concerns over increasing the frequency of elected abortion, to simple issues of maintaining quality controls standards in this hypothetical industry. Similarly, obtaining cells and tissues from living donors or cadavers is also not without ethical issues. For instance, an important and largely unresolved issue is whether it is morally acceptable to keep "deceased" individuals on life support for long periods of time in order to harvest organs as they are needed.

The implementation of ES-based technologies could address some of the ethical problems described above. First, it is important to note that the production of large

numbers of human ES cells would not in itself cause these same concerns in accessing human embryonic or fetal tissue, since the resulting cells have the potential to be grown for very long periods of time. Using only a limited number of human embryos not used during in vitro fertilization procedures, biotechnology could theoretically supply the needs of many millions of patients if the problem of histocompatibility could be resolved. Second, in the case of NT procedures, the patient may be at lower risk of complications in transplant rejection. Third, the only human cells used would be from the patient. Theoretically, the need to access tissue from other human beings could be reduced.

On March 4, 1997 President Clinton asked for a, "moratorium on the cloning of human beings until our Bioethics Advisory Commission and our entire nation have had a real chance to understand and debate the profound ethical implications of the latest advances." Prior to this 1997 request and the cloning of Dolly, Advanced Cell Technology had initiated research into the use of human somatic cell NT for human cell therapy (therapeutic cloning) and had obtained preliminary results that suggested the technology would be useful in treating disease. Following the President's request, however, the Company tabled all research in this area awaiting clarification of recommended guidelines. After internal review in 1998, the Company decided that it did not have sufficient data to assemble a scientific publication, but believed that it was in the public interest to release the preliminary results to promote an informed and reasoned public discussion of the issues. In this regard, we are grateful for the President's request of November 14, 1998 asking the National Bioethics Advisory Commission to analyze the issues surrounding this new technology.

In regard to the President's letter of November 14, 1998, we would like to offer the following observations. First, we share the President's concerns regarding the mixing of DNA across species. By way of background, it is useful to recall the debate surrounding the specter of mingling of human and non-human DNA in gene splicing technologies in the 1970s. In addition to the general discomfort of combining the genes of organisms across the plant and animal kingdoms, there were more focused concerns raised concerning the deliberate mixing of the genomes of viruses such as adenovirus and tumor viruses such as SV40 or between SV40 and bacteria such as E. coli for fear that new and virulent man-made pathogens may unintentionally result in a major health risk. Shortly thereafter, there were again concerns voiced over the mixing of antibiotic resistance genes in bacteria not then possessing such resistance. The resolution of those concerns may guide us in the consideration of these new technologies. The use of attenuated strains of host organism, and other precautions have served us well and allowed recombinant technology to advance and, in doing so, to improve the human condition.

Concerns over the mixing of the genomes of differing species is even of greater concern given newer technologies that allow the transfer of entire chromosomes across species. Given justifiable concerns that these technologies not be abused in medical research, we join in asking for ethical debate of the issue of the mixing of genomic DNA across species.

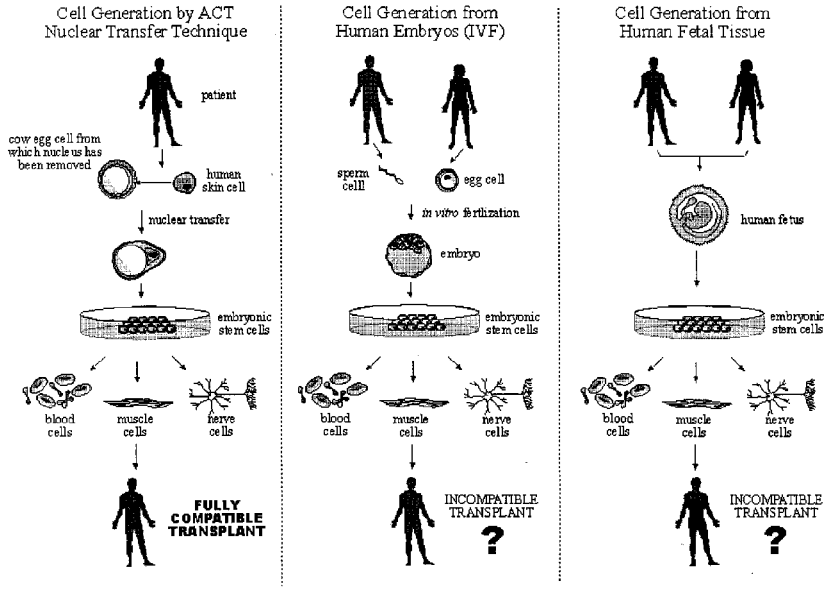
The mixing of DNA across species does not, however, bear on the issue of NT. The research performed in 1996 resulted in human cells with less than one millionth of the DNA being from a nonhuman (bovine) source, and that DNA was for the mitochondria, an energy source for the cell, not encoding species-specific traits such as eye color, intelligence, or other distinctive features. In addition, it was, and is, the intent of Advanced Cell Technology to produce fully-human stem cells through the genetic modification of the bovine egg cell to introduce human mitochondrial DNA.

The relevant issue is that the biotechnology industry is seeking guidelines for the application of ES and NT technologies in medicine. We believe that these new technologies, if properly applied, could lead to significant medical advances with life-saving potential. Poorly constructed legislation, designed to prohibit the cloning of a human being, could inadvertently interfere with urgent and ethical applications of the technologies in medicine.

Prohibitions against humanized surrogate NT may also have serious collateral consequences in addition to harming these new therapeutic avenues. During various in vitro protocols, it is not unlikely that human oocytes or embryos may be cultured in the presence of bovine proteins, such as bovine fetal calf serum. It would be unwise to set a precedent that the contact of a human embryonic cell with nonhuman (bovine) proteins is to be prohibited. Proteins do not encode hereditary information. The sensitivity remains in the area of mixing genomes (DNA) of human and animal, likely not the mixing of proteins, especially in the surrogate protocol under discussion wherein the bovine proteins are rapidly replaced by human.

We therefore respectfully request that Congress be measured and forward-thinking taking into full account the tools necessary for medical researchers to apply these exciting new technologies in clinical practice in the future.

Comparison of Methods for Generation of Human Embryonic Stem Cells



APPENDIX A

MICHAEL DAVID WEST, B.S., M.S., PH.D., CURRICULUM VITAE, SEPTEMBER 1998

Personal

Date and Place of Birth: April 28, 1953; Niles, Michigan.
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Education

Niles Senior High School; Niles, MI: 1971.
Rensselaer Polytechnic Institute; Troy, NY: B.S. Major: Psychology 1976; Minor: Management.
Andrews University; Berrien Springs, MI; M.S. Biology 1982.
Baylor College of Medicine; Houston, TX: Ph.D. Cell Biology 1989, (Division of Molecular Virology)

Business Experience

West Motor Leasing Company, Inc., President, General Manager, 1976–1982.
West Leasing Company, Inc., President, General Manager, 1978–1982.
West Motor Sales, Inc., President, General Manager, 1980–1982.
Geron Corporation, Founder, Director, Officer, 1990–1998.
Origen Therapeutics, Inc., Founder, Chairman, 1997-Present.
Advanced Cell Technology, Inc., President & CEO, 1998-Present.

Research and Professional Experience

1998-Present: President and CEO, Advanced Cell Technology, Inc., One Innovation Dr., Worcester, MA 01605.
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1994–1998: Founder and V.P. of New Technologies, Geron Corporation, 200 Constitution Dr., Menlo Park, CA 94025.

1993–1994: Founder and V.P. of Business Development, Geron Corporation, 200 Constitution Dr., Menlo Park, CA 94025.

1992–1993: Founder, VP, and Chief Scientific Officer, Geron Corporation, 200 Constitution Dr., Menlo Park, CA 94025.

1990–1992: Founder, President and CEO, Geron Corporation, 200 Constitution Dr., Menlo Park, CA 94025.

1990–1992: Senior Research Scientist, Department of Cell Biology and Neuroscience, Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, Texas 75235, Laboratories of: Dr. Woodring E. Wright, Dr. Jerry W. Shay.

1989–1990: Postdoctoral Research Fellow, Department of Cell Biology and Neuroscience, Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, Texas 75235, Laboratories of: Dr. Woodring E. Wright, Dr. Jerry W. Shay.

1985–1988: Graduate Student (Ph.D.), Baylor College of Medicine, Division of Molecular Virology, One Baylor Plaza, Houston, TX 77030.

1982–1985: Graduate Student (Doctoral Candidate), University of Arkansas for Medical Sciences, Department of Biochemistry, 4301 W. Markham, Little Rock, AR 72205.

1979–1982: Graduate Student (M.S.), Andrews University, Department of Biology, Berrien Springs, MI 49104.

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CURING DISEASE

Senator SPECTER. Dr. Varmus, we will begin the first round of questioning with you. There has been considerable discussion already about curing disease, dealing with life-threatening ailments, Parkinson's, heart disease, cancer, Alzheimer's. Are there any limitations as to the range of this kind of a technique on curing diseases? Would it apply to everything?

Dr. VARMUS. Well, Senator, it is a little difficult to answer the question because it is very difficult to know what science would be capable of producing. As you have heard from the——

Senator SPECTER. But the basic point is you find a way of replicating cells which are diseased. So would there be any apparent limitation on the scope of these technologies to cure any kind of a disease?

Dr. VARMUS. There would be certain kinds of diseases; for example, infections would not immediately be amenable to therapies with these cells. But as you have heard, one of the limitations that

currently exists is that, while we know that the cells in question can form many different kinds of tissues, we do not yet have the knowledge that allows us to efficiently differentiate them into the tissue of choice.

Moreover, as Dr. West just pointed out again and as others of us have alluded to, we do not yet have a clear solution to the problem of what we call histocompatibility, having tissues that can be delivered to any individual and not rejected by that individual's immune system. Indeed, the use of somatic cell nuclear transfer methods does offer promise in this regard and there is the potential for developing cell lines with pluripotent potential using that methodology.

Indeed, in last year's discussion of the Human Cloning Prohibition Act the President issued a statement of administration policy in which he wanted to preserve the ability to use somatic cell nuclear transfer with human cells for the purpose of developing stem cells for exactly this purpose. Of course, we view there to be a prohibition on that kind of research at the moment due to the amendment that I alluded to in our appropriation bill.

PARKINSON'S DISEASE

Senator SPECTER. Dr. Varmus, perhaps it would be helpful to take a specific ailment and to run through how this approach would, say, deal with Parkinson's. Could you use that illustratively to tell us what could be done to treat someone with Parkinson's?

Dr. VARMUS. As you know, Senator, Parkinson's is a result of loss of certain nerve cells in a region of the brain called the basal ganglia. Those cells are responsible for producing dopamine, an important neurotransmitter. There already are methodologies in use that attempt to restore brain function, for example by transplanting fetal cells to the brains of individuals with this disease, or by attempting to inactivate cells that usually inhibit the ability of other cells to produce dopamine.

You saw, still can see, a picture of nerve cells derived in Dr. Gearhart's experiments from his pluripotent stem cells. One could imagine being able to induce cells that specifically make dopamine and to introduce those cells using so-called stereotaxic instrumentation into the appropriate place in the brain to restore the function of that part of the nervous system.

Senator SPECTER. Well, how will the stem cell technique advance the current techniques used to deal with Parkinson's?

Dr. VARMUS. Well, the objective would be to be able to produce cells that are specifically designed to carry out the function of the cells that have undergone deterioration in the process of developing the disease. I cannot give you one, two, three yet, because obviously there is work to be done. But the point would be to have a large repertoire of cells that, rather than having to go and identify and having to use many fetal donors, essentially, one could have a bank of cells that is known to respond to certain kinds of chemical instructions to make the kinds of cells that would be useful in the transplantation process.

Senator SPECTER. One of the questions which those of us on this side of the panel always ask with respect to time line and cures is how much appropriations will set you in motion to find the an-

swer. But illustratively, is it possible to give a generalization, if this research were unleashed, how long it would take to find a cure, say to Parkinson's or Alzheimer's?

Dr. VARMUS. Well, remember, Senator, that I referred to the fact that certain kinds of stem cells are already in use in clinical practice, for example blood stem cells, and there are experimental models, especially in mice, that indicate that certain other tissues, like the heart, may be repaired by the use of cells that have been converted from committed stem cells to heart muscle cells using an appropriate recipe.

Given those precedents, it seems to me that within the course of the next decade or two, with an appropriate cadre of investigators, that many, many diseases would be at least treated, if not entirely cured, by the kinds of cell therapies we are talking about.

USE OF EMBRYOS

Senator SPECTER. My red light is on, but I am going to ask one final question of Dr. Thomson with respect to the embryos. There is the obvious concern of the use of embryos where an embryo could be the start of a human life. In your research in the use of embryos, how do you deal with this specific issue?

Dr. THOMSON. The embryos that we used were specifically made for clinical purposes, but they were beyond what the patients could use. The majority of these embryos had been frozen for a number of years and they had to decide what to do with them. The option that they were considering was to discard them, so it was a choice between discarding the embryos and doing this research.

Senator SPECTER. So what you are saying is that none of the embryos which you used had the possibility of being the start of a human life?

Dr. THOMSON. Because they would otherwise be discarded, yes.

Senator SPECTER. Because?

Dr. THOMSON. They would have otherwise been discarded.

Senator SPECTER. Otherwise been discarded.

Well, my time is up.

Senator Harkin.

FEDERAL BAN ON RESEARCH ON HUMAN EMBRYOS

Senator HARKIN. Mr. Chairman, thank you.

Since we have a limited amount of time, I have two things I want to kind of clear up. One kind of gets to the heart of the matter, I hope, here on whether or not the use of these stem cells are covered under the Federal ban that was placed here a couple of years ago on research on human embryos. Now, let me just read the law. It says: "None of the funds made available in this act may be used for: (1) the creation of a human embryo or embryos for research purposes." We're not talking about that here, is that clear? Is that right? "(2) Research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under pertinent sections of the Public Health Service Act."

Is that included here? "None of the funds made available under this act may be used for research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of in-

jury or death greater than that allowed for research on fetuses in utero under 45 CFR,'' et cetera, et cetera.

Now, let me read the next paragraph: ''B. For purposes of this section, the term' human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 as of the date of enactment of this act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.''

My point is this. It says: ''For purposes of this section, the term' human embryo or embryos' includes any organism.'' Now, I heard someone say that these stem cells are not organisms. Now, so I asked my staff to get me the dictionary. I want to find out what an ''organism'' is. In this dictionary, Random House—maybe it is different in some others—it says: ''Organism. 1. A form of life composed of mutually dependent parts that maintain various vital processes.''

Now, to my limited scientific knowledge, that definition does not meet a stem cell. It does not seem that a stem cell contains ''mutually dependent parts that maintain various vital processes.''

So my question is, getting back to the matter of whether or not these are covered by the ban on Federal human embryo research: One, are these organisms? Are these stem cells organisms? I am just asking. Anybody? Dr. West?

Dr. WEST. The cultured cells I would say are not. If they are, for instance, grown in a laboratory dish or transplanted into a uterus, they will not form a human being. They have never been observed to form a complete animal using the animal equivalent of these cells.

Senator HARKIN. Dr. Varmus.

Dr. VARMUS. As a scientist, as I have testified here today from the perspective that I bring to this from my professional background, I agree that these are not organisms. The issue that we are dealing with in the Government is complying with the law, knowing the legal definition of an organism, and we are struggling with this as part of the activities in the Department and elsewhere in the administration to be sure that any actions we take in response to these developments are in compliance with existing law.

Senator HARKIN. I understand.

Dr. Thomson, are these organisms?

Dr. THOMSON. They are not organisms and they are not embryos.

Senator HARKIN. They are not organisms?

Dr. THOMSON. Or embryos, no.

Senator HARKIN. Or embryos.

Dr. GEARHART. No; they are not. They are not organisms.

Senator HARKIN. They are not organisms.

Well, I may not be a very good scientist, but I am somewhat of a lawyer and I do read the English language. It says: ''For the purposes of this section, the term 'human embryo or embryos' includes any organism.'' If it is not an organism then it is not included.

So that is why I made the statement that I did at the opening of this session. From my reading of it and my understanding of it, this is not covered by the Federal ban. If someone has a different definition of ''organism'' I would like to see it.

Second, during the debate last year on human cloning the National Conference of Catholic Bishops cited a number of alternative ways to conduct research using stem cells, alternatives they said would not require the use of a human embryo at all. They include: (A) stimulating proliferation and differentiation of the quiescent stem cells which are known to exist in many adult tissues and customizing those cells to each individual patient; (B) collecting stem cells from bone marrow or umbilical cord blood or collecting stem cells from fetal bone marrow; (C) genetically engineering cells of different kinds to repair damaged organs, perhaps by injecting them with an oncogene.

Do any of you know of this research? Is it possible to achieve the same therapies with these alternatives? I am not a scientist. I do not understand this.

Dr. VARMUS. Senator, in my testimony I alluded to the fact that there was a tremendous amount of research already supported by the NIH and by private industry and many other countries on stem cells that exist in fetal and adult tissue that has the potential to develop into specific types of cells. We think this is very important research. Indeed, it has produced many of the advances in transplantation of bone marrow and reconstitution of bone marrow that is used daily in hospitals. So we strongly endorse that approach.

What is at issue, though, is the tremendous potential for working with cells that are earlier in that hierarchy of stem cells that I described to you earlier. Certain fundamental questions about how cells differentiate, how we become complex organisms, how birth defects arise, what causes cancer, how cells fail, tools for use in development of new pharmaceuticals, the ability to expand the repertoire of cells that can be used for tissue therapies, is in my view going to have to be approached with cells that come from organisms earlier in development.

Now, as I have also tried to indicate, research with such cells does create ethical concerns and we need to address those and balance those against the benefits.

Senator HARKIN. I understand. I think what is important here is that when I read the news accounts and the newspaper stories they say stem cells as if every stem cell is exactly the same.

Dr. VARMUS. That is wrong.

Senator HARKIN. That is wrong. We have to clear that up here today for the public. When you are talking about stem cells you are talking about a broad spectrum of stem cells.

Dr. VARMUS. That is correct.

Senator HARKIN. Yes?

Dr. WEST. We call them stem cells maybe in part because it is a bit like a tree. The stem cells we are talking about today are at the base of the development tree and can branch out into all the different cells and tissues of the body. Some stem cells are way out at the edges of the branches and can only become a few different cell types. There are many cell types. There are tissues in the body that have no stem cells.

Heart tissue, the leading cause of death in the United States, there are no stem cells to repopulate the heart. They simply do not exist. But, going back to the base of the developmental tree, we be-

lieve we can potentially make heart muscle cells that can be used to address the No. 1 cause of mortality.

Senator HARKIN. I thought that was important to clarify.

Thank you.

TREATING AGE-RELATED DEGENERATIVE DISEASES

Senator SPECTER. Thank you, Senator Harkin.

We are going to take another round here and try to hold it just to the five and five, because we do have quite an array of other witnesses.

Dr. West, you used the phrase that the technique would make cells young and would certainly be a retarding of the aging factor. Just how far could this go? Do we really have what could be a realistic fountain of youth by the use of this technique?

Dr. WEST. I think a fountain of youth may be a bit of a stretch. But what we do have published information on is that the process of nuclear transfer does impart back to an aged cell the full proliferative capacity it had when it was born. Dolly, after all, was born as a young lamb, not an old one.

Senator SPECTER. So what are the limitations which would stop it from being a veritable fountain of youth?

Dr. WEST. I am excited about the possibilities of using somatic cell nuclear transfer to treat age-related degenerative disease. There is now growing evidence that in numerous diseases associated with aging that there are cells that have lost the potential to proliferate in the way that they did when they were young, and so nuclear transfer could be used to treat immunosenescence, the aging of our immune system. The elderly increasingly find it difficult to fight infectious disease, chronic pneumonias, and other things.

So the nuclear transfer has the potential to benefit embryonic stem cell research in personalizing these cells—they are genetically identical to you—eliminating actually many ethical problems associated with sourcing cells and tissues today. As you know, the FDA is reviewing possibilities of making cells and tissues in animals, xenografts, taking pig kidneys and pig heart valves and so on, and sourcing cells and tissues from cadavers, keeping people alive to source cells and tissues.

CLONING

Senator SPECTER. Dr. West, let me just interrupt you, if I might, because we have very limited time, and ask you this one other question. Your company's technique has been characterized as the use of cloning techniques to create an embryo out of human and cow cells. Is that accurate with respect to the characterization of cloning?

Dr. WEST. I think it is very inaccurate. Actually, the cartoons that show the half-human, half-cow I think are science fiction. The goal here is to use the proteins in the egg after the genomic information is removed to reprogram a human cell.

Senator SPECTER. When you use the human and cow cells, eyebrows are raised. What concerns do you have about the joinder of human and cow cells?

Dr. WEST. I actually agree with the President's letter of November 14, where he asked the National Bioethics Advisory Commission to look into this issue of the mixing of species. It has been a profound debate for years in the scientific community. As you know, the recombinant DNA debate of the 1970's was a debate about the mixing of DNA across species, and this is even more profound today. We have the ability today to actually introduce whole chromosomes across species, not single genes.

PARKINSON'S DISEASE

Senator SPECTER. Dr. Gearhart, what kind of a time line do you see on the kind of research you have done to provide practical answers to problems like Parkinson's or Alzheimer's or cancer?

Dr. GEARHART. Actually, I think Parkinson's will be one of the first targets and one that we will see in a short period.

Senator SPECTER. How long is a short period?

Dr. GEARHART. Well now, let me back off.

Senator SPECTER. No, no; go on.

Dr. GEARHART. I will. I actually think within several years, to be honest with you, because these neurons that I have demonstrated here, we do not know, to be honest, since this is new data, we do not know what neurons they represent, what type, whether they are cholinergic, dopaminergic, etcetera.

But from what we have known from our colleagues' work who are studying the differentiation of neurons in animals, the dopaminergic neurons are one of the first ones that are developed. We know more, I think, about what factors actually result or will lead to the formation of a dopaminergic neuron.

Senator SPECTER. Dr. Gearhart, I want to get a fairly short answer from doctor—did you want to say something?

Dr. GEARHART. I should have explained dopaminergic neuron, which is the neuron that is deficient in Parkinson's.

Senator SPECTER. I want to get a brief answer from Dr. Thomson and Dr. West on time line for practical application before the red light goes on.

Dr. THOMSON. There are practical applications even today, not in therapeutics right away. But for example, for making heart muscle cells, there are very simple techniques to do this in mouse embryonic stem cells and they will probably transfer fairly quickly to human embryonic stem cells.

Senator SPECTER. Applicable today?

Dr. THOMSON. Applicable today, because you can use them for drug screens.

Senator SPECTER. Illustratively, for Parkinson's how long?

Dr. THOMSON. Parkinson's? I am going to say 5 to 10 years more. It will be one of the first ones.

Senator SPECTER. Dr. West, what time line do you see?

Dr. WEST. I would estimate for the discovery of drugs, using the cells simply to discover drugs in the laboratory, 3 to 5 years; for the first cell therapies, somewhere between 7 to 15 and 20 years; Parkinson's potentially beginning within 7 to 12 years.

Senator SPECTER. Thank you.

Senator Harkin.

Senator HARKIN. That is very encouraging. What I hear you saying is that if this basic research is allowed to go forward that a minimal amount of understanding of how stem cells develop will lead to a proliferation of knowledge, which then can be used by a lot of scientists all over the field. Is that sort of—am I thinking the right way?

Yet, if you block this basic understanding of how that stem cell differentiates, that means that all those scientists out there cannot then focus on how to apply it in that timeframe. Am I close to it? Something like that?

So that is why I am grateful the chairman has called this hearing, because of the misinformation I think is out there, especially regarding the ES technologies, and the misinformation as to whether or not this is really covered by the law banning human embryo research.

Let me focus a little bit—now, you talked about this time line that the chairman just laid down in terms of Parkinson's. What I heard was that anywhere from 3 to 5 to 12 years, somewhere in there we might be finding something. Is that assuming the Federal ban continues and this research is not allowed to go forward, or that it is federally funded and only—hold on I need to back up.

You can do this research in the private field. NIH cannot fund it. What I heard all of you say is that it would be vitally important, to have NIH be able to fund it. If this Federal ban is deemed to cover research on stem cells, does your time line hold?

Dr. WEST. The time line I gave, 7 to 12 years for Parkinson's, assumed that the NIH would be allowed to fund research in differentiating these cells into cells for Parkinson's.

Senator HARKIN. So your answers were based on——

Dr. WEST. Yes.

Senator HARKIN [continuing]. I should not say lifting the ban because, you see, I do not think the ban applies.

Dr. WEST. Right.

Senator HARKIN. So I have got to be careful about what I say. So your time line is based upon an interpretation or reading of this that the ban does not apply to stem cells?

Dr. WEST. Right.

Senator HARKIN. Is that true of all of you?

Dr. VARMUS. That is correct.

Dr. THOMSON. That is correct, but also the number of diseases likely to be treated by this will increase exponentially if there is public funding. Industry can target one or two or a couple and get it done in a reasonable time. The more difficult ones will just be left undone.

DIABETES

Senator HARKIN. So you are saying, again, with this research there could be all kinds of breakthroughs later.

Dr. THOMSON. Take diabetes as an example. Take diabetes as an example. That is caused by the death of a very particular cell in the pancreas and it is a fairly difficult developmental program to go from undifferentiated stem cell to beta islet cell. That is likely to be a more difficult cell to derive from embryonic stem cell. It re-

quires a lot of basic research, and the Government has the job of doing basic research.

Senator HARKIN. Well, I think there is so much potential here. But there is so much misinformation out there, the cartoons of the half-horse and the half-human, going back to Greek mythology. I think we have been burdened with Greek mythology for far too long. [Laughter.]

Senator HARKIN [continuing]. And we have to get past that.

But our job I think as legislators—and again I compliment the chairman; I thank him for having this hearing—is to try to get over these hurdles of misinformation that are out there. And I can understand people having these fears based upon inadequate knowledge and understanding of what you are doing.

I think our job is to make sure that we get that understanding out there in a clear fashion.

So I compliment you all for the work you are doing. I believe that if this research is allowed to go forward it is the gateway to a lot more understanding of how we treat illnesses, especially genetic illnesses. Now, how the proper way is, whether it is NT-based, nuclear transfer-based, or the ES-based, I do not know. That is way above my pay grade. But I think in either case the Federal ban certainly does not apply.

I thank you for your work and I encourage you to press on, and hopefully we will have a clearing up of this so that NIH, Dr. Varmus, can move ahead very aggressively in this area. I would close on that question: If, in fact, this is the case, will NIH move ahead aggressively?

Dr. VARMUS. We will certainly do so, with, of course, the usual oversight. That is, we will have a panel, we will have guidelines, we will have the review of grant applications, and proceed as we did on previous topics, like recombinant DNA or gene therapy and xenotransplantation, with due consideration of the ethical issues and firm oversight of the science.

Senator HARKIN. Thank you, Dr. Varmus.

Senator SPECTER. Thank you very much for your testimony, gentlemen. I think that it has been very useful in shedding light on the issue that the embryos which are used here are not embryos which could produce life, that when we talk about fetal tissue, as Dr. Gearhart has talked about it, it is discarded fetal tissue, it is not related to any inducement of abortions or any medical procedure to produce fetal tissue.

Dr. GEARHART. That is correct.

Senator SPECTER. But there is concern, as Dr. West has described, for the cloning consideration and for the mixture of cows and human cells, and, perhaps most importantly, the projection as to when immediate practical application may be present. Dr. Thomson points out that with certain heart cells it is now.

It is obviously a heart-rendering situation to see people with Alzheimer's. We just had a very difficult situation in a Veterans Administration hospital in Coatsville, PA, where people with Alzheimer's, veterans, who could not walk were being excluded from treatment. We finally got that solved. People with Parkinson's had a major event in Pittsburgh last year with Muhamed Ali coming

forward and people with the Parkinson's ailment. One man has an hour glass that he measures his time by.

And as we work through juvenile diabetes, and this subcommittee is deluged with people who want more funding and more answers and more responses to their medical problems. We did the maximum last year with $2 billion. Senator Harkin and I do not know what we can do for an encore this year.

But when you talk about medical research which may provide very, very unique answers with all the people who are suffering there, we want to see what the medical potential is. It appears to be very, very promising for catastrophic illnesses.

We are now about to turn to a panel to deal with the ethical considerations, the other side of the coin. So we very much appreciate your coming, and now we will call panel two.

Senator HARKIN. I am sorry, there is one other point I just have to clear up. Could I just clear up one thing?

Senator SPECTER. One final question.

Senator HARKIN. I have to clear up something. I want to ask you a question. I am drafting a letter of my own to Dr. Shapiro, but the letter that the President wrote said: "I am deeply troubled by this news of experiments involving the mingling of human and nonhuman species."

What you are saying, Dr. West, is that that is not scientifically correct?

Dr. WEST. Well, I share his concern about the mingling of genomic DNA. That is not what we are doing.

Senator HARKIN. That is right. I would share that concern, too, combining genomic DNA. I would share that, too. But you are saying that that is not happening?

Dr. WEST. That is not what we are doing.

Senator HARKIN. I just wanted to clear that up.

Dr. VARMUS. We also want to focus on the question of whether experiments are being conducted in cultured cells as opposed to experiments that would involve any attempt to return a potential embryonic cell to a womb to develop a mature individual. That is a very important distinction that was repeatedly made by my embryo research panel when they considered these experimental approaches.

Senator HARKIN. Thank you very much.

Thank you, Mr. Chairman.

Senator SPECTER. Thank you very much, gentlemen.

STATEMENT OF ARTHUR L. CAPLAN, Ph.D., DIRECTOR, CENTER FOR BIOETHICS, UNIVERSITY OF PENNSYLVANIA

Senator SPECTER. We would now like to call Dr. Caplan, Dr. Doerflinger, Dr. Okarma; and we are going to bring Dr. Meslin in on the next panel, all together.

Our first witness is Dr. Arthur Caplan, first witness on the second panel, who is director of the Center for Bioethics at the University of Pennsylvania, had that position since 1994; also serves as the chairman of the advisory committee to the Department of Health and Human Services Centers for Disease Control and Food and Drug Administration on Blood Safety and Availability. Ph.D.,

from Columbia, author of some 400 articles in professional journals.

Welcome, Dr. Caplan. The 5-minute rule is in effect and the floor is yours.

Dr. CAPLAN. Thank you, Senator.

I have to say, too, that you have made the people at the legislative liaison office at the University of Pennsylvania very happy with your announcement about staying on this committee. They will be more interested in that than anything I have to say here.

When I left this morning I was trying to look at some books, as philosophers such as myself are wont to do, about ethical ideas. I did look a little bit at the Greek myths. I am not as skeptical as Senator Harkin that Greek mythology is useless, since to some extent the Greeks kept going with great zeal in trying to advance what we call science today, though they tried to warn us about not being full of hubris and pride when we did it.

I looked at some other ethics books on my shelf, but I realized that the real source of my knowledge about what is right and wrong is to ask my 14-year-old son. So I sat him down and I said: Now, I am going down to Washington. The issue is, if we try hard to respect human origins and try hard to respect human embryos and try hard to understand the special nature of procreation, if we have a technology that offers us benefits, that might help the paralyzed, the disabled, people dying of heart disease and other dread ailments, how do you think we should trade this off?

My son said, "Well, dad, it seems to me if you have got a man in a wheelchair you owe that person something in the here and now, as opposed to trying hard to respect what might be or what could have been, what is potential."

I think he is right. I think it is true that the goal of our public policy should be to tell that person in a wheelchair we are going to try and weigh tradeoffs morally, ethically, between the hard choices that have to be made in using certain tissues, certain cells as sources, dealing with certain totipotent and pluripotent cells as points of origin for making wondrous therapies, and that it is wrong in the end if we cannot come up with a policy that says we will not hold that person in a wheelchair hostage to our moral concerns about tissues that will otherwise be destroyed, tissues that are not going to be turned into human beings under any circumstances, or cells and tissues that, because we misunderstand or misdescribe them, are going to wind up being misclassified as potential people or possible human beings.

We have heard about that in the first panel and I think that is the goal that faces Congress and the executive branch, is to try and get us into the right balance.

The other introductory thing I would like to say is just that I find myself as a philosopher, someone interested in ethics, amazed by these developments this past year, 2 years, ranging from cloning and creation of origin cells, oocytes from animals that might be places where animal sources can be used to host the production of human proteins, and stem cell developments.

It reminds me that we do not live in a world of moral absolutes. Some of the bright lines that we think we can go to are not so bright when the DNA of any cell can be converted ultimately, po-

tentially, to a human being by transfer and technology that allows for nuclear cell cloning. We can no longer say that we understand exactly when life begins, how to respect life, depending upon certain properties that might inhere in particular cells or tissues.

It seems to me in the end that what we have got to do is this. We have to say that some principles ought guide us as we move forward in this area, and I want to propose four, and I think they are ones that guide all medical research.

The first is that we should seek to achieve the most good or benefit with the least harm and destruction of things that we value. I believe that we do value human procreation, human origins, human embryos, and we want to try and minimize what we have to do there to get benefit, but we must pursue benefit.

That tradeoffs to achieve progress in the struggle against disease and disability are inevitable and they are ethical. We do that every day, Senators, when we conduct human research and understand that we put people at risk, that deaths will result from some of the things that are tried, that we may hasten death inadvertently. We understand that tradeoffs must be made, and I think that applies in this area.

It seems to me that the creation of materials with the capacity to become human life is a process that requires moral guidance and humility. That is something that I think we are going to have to inject in this debate.

The last principle I would like to advance is that it is better to do things in this area that are accountable and public than it is to ask them to become private and commercial. If we continue the policies we have, we are not going to be able to bring the nuanced supervision and oversight that this area of stem cell research requires from us.

PREPARED STATEMENT

I want to end by saying again, I do not think we are in the realm of absolutes. I think we need judgment. I think we need virtues. That is why we need public funding, public accountability, to make the right tradeoffs.

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

[The statement follows:]

PREPARED STATEMENT OF ARTHUR L. CAPLAN

THE ETHICS OF HUMAN STEM CELL RESEARCH

Why is stem cell research so important?

Tremendous fanfare has greeted the announcement of success in identifying human embryonic stem cells. Fanfare is becoming an increasingly common phenomenon in the world of science and biomedical news. So there is a tendency to greet each weeks 'breakthrough' with some cynicism. But in the case of the isolation of pluripotent embryonic stem cells the acclaim is surely merited.

The identification of human embryonic stem cells has been widely acknowledged as of inestimable value because it will help scientists understand basic mechanisms of embryo development and gene regulation. It also holds the promise of allowing the development of techniques for manipulating, growing and cloning these cells to permit the creation of designer cells and tissues. The availability of immortal stem cell lines will greatly aid drug discovery. The study of stem cells should also shed light on the process of human fertility and growth and should even open the door to techniques that could be used, someday, to permit many forms of genetic engineering and transplant therapy for human beings.

There are many in the biomedical community who, when confronting such powerful and useful possibilities maintain that no steps or actions should be taken to restrict, control much less prohibit this important research from moving forward. There is even the suggestion that anyone who raises questions about the ethics of human embryo stem cell research is merely using the prospect of research in this area for "political" purposes.

Such objections are rhetorically powerful but not at all persuasive. As many scientists, policy makers, religious leaders and the American people have long understood, research that may lead to the elucidation of the secrets of human reproduction and development, the modification of the genetic makeup of future children and their children, the creation of new forms of life and a bounty of therapies that hold out the prospect of a longer and better life raises issues of ethics and social policy that must be discussed and debated publicly. It is very appropriate that these issues be raised and examined since human embryonic stem cell research is in its infancy and there is still time to shape and direct its course.

Ironically, the much of the work being done on human embryonic stem cells is being done without the support of funding from American governmental agencies. This is entirely due to ethical concerns about any research involving human embryos and tissues derived from elective abortions. Embryonic stem cell research has and may involve these sources.

Many worry that to raise any questions about the ethics of stem cell research is to sacrifice a crucially important and incalculably valuable area of biomedical research on the alter of the abortion controversy. They also despair that any dialogue can occur in our society about the ethics of using materials derived or created from embryonic sources given the horrid track record of social divisiveness and violence that are the constant companions of any discussion of abortion in this country,

But the reality is that unless some effort is made to address head on the moral and social issues that embryo stem cell research raises it is very likely that further advances in this area will be slowed as a result of a lack of government support or because they will be conducted completely under private auspices with little accountability and relatively little accessibility to the community of biomedical science. The value of embryonic stem cell research is simply too great to permit a policy stance of inaction to be the response that our government and other governments around the world offer to this enormously promising domain of inquiry.

KEY ETHICAL ISSUES RAISED BY STEM CELL RESEARCH.

Sources

The most obvious and pressing issue raised by stem cell research is the issue of the source of these cells. Stem cells can be obtained from human embryos specially created for research purposes, they can be obtained from aborted fetal tissues including both spontaneous and elective abortions, they can be created by processes that involve the transfer of genetic materials to either animal or human egg or embryo hosts and they can be obtained from embryos created through various means of artificial reproduction and then frozen either as no longer wanted by the persons whose gametes created them, or, being held as reserves for the future by couples seeking to have children. What is fascinating about these many sources of human embryonic stem cells from an ethical point of view is that they are not at all morally equivalent.

Not all embryos are created equally

Specially created embryos

The moral problems with making embryos for research are that as a society we do not want to see embryos treated as products or mere objects for fear that we will cheapen the value of parenting, risk the commercialization of procreation, and trivialize the act of procreation. It is the moral framework that society wishes to construct for procreation and reproduction, and the interests of those whose gametes are involved in making embryos, that provide much of the moral force for restricting or prohibiting the manufacture of embryos for nonprocreative uses. This is especially so once it is realized that most human embryos at the point of conception will not become human beings even under the best of all possible developmental circumstances. Those who study the problem of infertility are beginning to understand what it is about certain eggs and embryos that make them unlikely or unable to develop into fetuses and later babies. While it is true as a matter of historical fact that all human life has begun with conception it is not true that all conception is capable of becoming human life. Nor will it be true for long that all human life must begin with conception. These changing realities mean that much more fine-tuned

and nuanced conceptual framework is needed to keep pace with advances in knowledge and manipulability of human gametes and embryos.

The moral problems with making embryos for research are that as a society we do not want to see embryos treated as products or mere objects for fear that we will cheapen the value of parenting, risk the commercialization of procreation, and trivialize the act of procreation. Society may or may not agree that a human conceptus is deserving of full ethical standing and respect on a par with an adult human being. But, surely we do have a broad consensus in American society that the process of creating embryos that have the potential and ability to become human beings requires special status and standing within our law and our culture.

If that is so then the manufacture of embryos for stem cell research will have the potential to become persons may be morally suspect because it violates our desire to accord special standing and status to human conception, procreation and sexuality. To do nothing in this area it should be noted is to consign the practice of embryo creation for generating stem cells to the marketplace which is to completely abrogate any special standing or status to human conception and procreation.

Spare embryos

One of the greatest ironies of current policies governing embryo research in the United States is that it has created a situation in which a huge industry has arisen to treat infertility with relatively little oversight and accountability for its practices. It has also created a situation in which the demand for clinical services is high but the knowledge base of those providing techniques such as in vitro fertilization (IVF) is not what it might be because of the lack of Federal funds to support fundamental research. As a result, when couples seek to use IVF they are required to create more embryos than they or their doctors might wish in order to minimize the need to create more should they fail to have a child and to help insure that at least some embryos will be made that are capable of growth and development. This means that some fortunate couples are lucky enough to have the technique work on a first or second try but wind up with the problem of what to do with remaining surplus or spare embryos. This country now finds itself in a situation in which tens of thousands of orphan embryos sit in liquid nitrogen unwanted and highly unlikely to be used by anyone ever to try to make babies.

Recently the United Kingdom enacted legislation to permit the destruction of unclaimed and unwanted embryos. The United States has not done so but there are thousands of embryos that might be made available for research and study for many purposes including stem cell research if those who created them were given this option or if clinics could make them available for this purpose after a waiting period of say ten years.

There are some who would still object that these frozen embryos are still potential persons. But that claim does not square with the facts. If no woman is willing to have the embryos placed inside her bodies, if clinics are reluctant to use embryos that have been stored for long periods of time because their potential to become babies is diminished or if couples do not want anyone else using their embryos then their potential for becoming persons is zero.

There would be a moral problem if embryos were created solely for the purpose of being frozen and then used for research. Such a practice would demean human reproduction and sexuality in turning it into a process of manufacture and mass production. But, it is very simple to prevent such practices from occurring. If infertility clinic personnel understood that it was illegal and punishable by fine and prison to inquire if a couple or woman wanted to freeze embryos until an IVF cycle had been completed, then there would be no incentive to create embryos. Spare, unwanted or damaged embryos could then be made available for stem cell research, storage with consent or future utilization.

To those who say this is still permitting the use of human embryos for a purpose that is disrespectful, research and the consequent destruction of the embryo, it seems appropriate to ask why continued freezing is not just as disrespectful. It is also appropriate to ask why, even if regrettable and sad, it would not be worth permitting the donation of spare embryos for research that might lead to cures and benefits in much the same way that we allow families to donate their loved ones organs and tissues under the most tragic of circumstances to aid others? Spare embryos would seem to be a legitimate and morally defensible source of human embryonic stem cells.

Constructions

Perhaps the most disturbing source of stem cells is from embryos that are specially built or designed for this purpose. Chimeras, human-animal mixtures believed capable of prolonged development from conception, possibly to birth, fused cells

using enucleating human or animal eggs and genomic transfer, disabled oocytes or embryos made from disabled sperm are but a number of possible ways in which scientists might create new forms of embryos to generate embryonic stem cells. The ethically positive side of this kind of construction is that it may be possible to create useful stem cells without having to use embryos that have any potential to become persons. The negative side is that the creation of special embryonic constructs may involve the creation of potential whose outcome is uncertain, unknown or would have the potential to create a severely deformed and damaged living organism. The complexities in this area require a nuanced moral response but it does seem clear that a clear boundary line must be to prohibit the creation of any living being that would with certain become or have the potential to become a deformed, damaged, freakish or dying entity. There are also other risk involved with some forms of construction that take human genomic material into animal hosts or vice versa. These include the danger of importing viral matter or sub-viral entities into the human population. There are also risk that some material may then be carried into stem cells made from such sources.

SOME POSSIBLE MORAL PRINCIPLES TO GUIDE STEM CELL RESEARCH

It might be helpful once it is recognized that there are no hard and fast lines to be drawn with respect to the ethics of stem cell research to try and advance some simple moral principles that might help those charged with controlling or approving such research. I would suggest the following as principles which are in evidence already in other areas of biomedical research and therapy:

—Seek to achieve the most good or benefit with the Least harm and destruction of things of value

—Tradeoffs to achieve progress in the struggle against disease and disability are both inevitable and ethical

—The creation of materials with the capacity to become human life is a process that requires moral guidance and humility.

—The complexity of the tradeoffs involved when research is being conducted at the boundaries of human life requires accountability and publicity.

Each of these principles is used to justify activity in biomedical research and therapy that is known to be risky or even known to be harmful but which has important benefits to individuals and society. Our society is quite familiar with the concept of tradeoffs. Americans recognize few moral absolutes and in the area of stem cell research where the tradeoffs frequently involve the possibility of harm to potential persons versus the reality of harm to real flesh and blood persons it is hard not to use some of these principles to guide prudent choices, albeit tragic ones. To be blunt it would be hard to honor principles such as these and the role they play in biomedicine and many areas of public life and still tell the persons paralyzed in a wheelchair or immobile as a consequence of ALS or Muscular Dystrophy or Parkinson's that they must remain in such states because of inviolate moral concern for the moral standing of an unwanted frozen embryo.

PUBLIC VERSUS PRIVATELY SPONSORED RESEARCH

Perhaps the most neglected factor in weighing what to do with respect to stem cell research is the reality that stem cell research will proceed even without federal funding. It will proceed more slowly but it will proceed. It will proceed with no accountability but it will proceed. It will proceed cloaked in secrecy but it will proceed. And it will proceed with an eye toward the commercially attractive rather then basic knowledge or the public good but it will proceed. The importance of the benefits to be garnered in this area makes it imperative that speed, accountability, publicity, and the drive to understand shape as much of the early course of stem cell research as is possible. Add to this the fact that the world of embryo sources and the status of stem cells themselves is complex and it becomes certain that it would be better to see publicly sponsored research complement private activities and publicly accountable oversight accompany the market ethos that soon will prevail in the United States if no action is taken by government.

A BRIEF HISTORY OF POLICY RESPONSE TO THE ETHICS OF EMBRYO RESEARCH

Announced with great fanfare, the Acting Director of NIH established a panel to recommend guidelines for the funding of preimplantation embryo research in August 1993. The Human Embryo Research Panel was composed of 19 members, including 11 researchers, scientists and physicians, 4 ethicists, 2 lawyers and 2 public members. It met in public six times from February to September 1994, when it issued its final report. The panel's charge was to place potential research involving the ex utero preimplantation human embryos into one of three categories: (1) accept-

able for federal funding; (2) warrant additional review; and (3) unacceptable for federal funding.

Using the mechanism of majority vote, the panel concluded that studies to improve chances of pregnancy; research on fertilization; research on egg activation, maturation and freezing; preimplantation genetic diagnosis; development of embryonic stem cells; and creation of parthenotes were acceptable for federal funding. Unacceptable research included cloning and use of fetal oocytes followed by transfer to a female uterus, and cross-species fertilization. This panel's recommendations have been more or less ignored by the NIH Director, Congress and the President ever since.

The reason why is that the moral foundation for the panel's recommendations about embryo research was not persuasive. Unless a moral framework emerges that proponents and critics of embryo research can accept, it is likely that policy recommendations about stem cell research will meet the same fate. This ought not be allowed to happen since the scientific, therapeutic and commercial benefits of stem cell research are too enormous to reject or hinder simply as a result of an inability to confront a tough ethical problem head on.

WHY WAS THE MORAL FRAMEWORK USED TO SUPPORT SOME EMBRYO RESEARCH UNSATISFACTORY?

The panel considered and rejected the moral stance that a human embryo has rights that would completely prohibit its use in research. To those who argue that an embryo is a human person from the moment of conception, the panel responded that there is no single trait or property present at conception that suffices to confer personhood, and thus, rights, on an embryo.

Having rejected rights as the proper framework for thinking about the moral status of the human embryo, the panel recommended the adoption of what it termed "a pluralistic approach." Embryos possess "a variety of distinct, intersecting and mutually supporting considerations such as "genetic uniqueness, potentiality for full development, sentience, brain activity, and degree of cognitive development". The panel argued that "their developing presence in an entity increases its moral status until, at some point, full and equal protectability is required." In essence the panel recommended a 'big tent' solution.

But, the pluralistic framework was not and is not persuasive. Just saying embryos have a lot of potential and many different emerging properties leaves matters mysterious and unresolved. It is not clear what properties of embryos confer moral standing or worth and which are simply properties that are interesting but irrelevant to ethics. Without more of an underlying rationale for why particular property or set of properties are morally important, the panel's framework wound up looking like it was constructed to rationalize a desired conclusion—that some research on embryos ought to be permitted—rather than as a conclusion which follows from an ethical analysis.

The failure to be persuasive about the moral status of the embryo turned out to be a crucial failure of the report. Saying that embryos have a combination of properties which somehow entitle them to respect without explaining how those properties confer moral significance on embryos or what it means to say an embryo ought to be treated with respect leaves policy makers and ultimately biomedical scientists with little to work with in terms of moral guidance.

What the earlier panel which took on the analysis of the ethics of embryo research did not grasp is that the human embryo has moral standing not so much for what it is at the moment of conception, but because the embryo is the result of procreative activity which is intended to produce or is at least capable of producing a child. This means that for many embryos there are other human beings who have a direct interest in the status and fate of the human embryo since their gametes created it, it carries their genes and potentially could become their child. It also means that the key moral characteristics of human embryos are not their inherent properties but the potential that they have to become persons and the intent that those who created them have to permit those which can do so to do so.

The same analysis is true but only more so for human embryonic stem cells. Some of these cells come from embryos which had the capacity to become persons. Some may be located and studied in embryos that lack any such capability. Some stem cells will originate in embryos which have no prospect of becoming persons because they are slated for immediate destruction. And still other stem cells might originate in embryos which were intentionally created so as to lack the ability to become a person under any circumstances. To simply ban all stem cell research as immoral because it relies on human embryos of some sort as the source of such cells is to conflate what are fundamentally different embryos with different moral standing.

And to equate stem cells themselves with human embryos capable of becoming persons is to commit the same conceptual mistake but only in a more flagrant form.

In order to understand what is and is not ethical with respect to stem cell research it is necessary to know a great deal about the nature of the human embryo where such cells must be identified and isolated, something about the stem cells themselves, something about the aims and goals of the research and something about the benefits that are likely to eventuate from a particular research study. Simple moral schemes of classification are not sufficient for negotiating this dense biological terrain. It will take a committee or commission with the time and expertise to review particular proposals from specific researchers to make the judgements that are required.

WHAT SHOULD BE DONE?

I conclude with three recommendations based on my understanding of the nature of the issues raised by stem cell research and the complexity of ethical and social questions such research raises:

1. America needs to create a public forum where advances in biology and genetics can be discussed by ethicists, philosophers, theologians and other humanists and social thinkers so as to permit a richer set of concepts and categories to emerge so as to enhance public and political understanding of what it is to talk of the creation of human life, new forms of life and potential life.

2. America needs to seek to allow the many benefits of stem cell research to be secured. This does not however make moral discussion of how to proceed simply political. Nor does it mean that concerns and worries about the moral licitness of stem cell and embryo research must always yield to the promise of benefits and new knowledge.

3. America needs to create an oversight body, committee or commission with appropriate expertise to consider and approve requests for research protocols involving stem cell and embryo research.

STATEMENT OF RICHARD M. DOERFLINGER, ASSOCIATE DIRECTOR FOR POLICY DEVELOPMENT, SECRETARIAT FOR PRO-LIFE ACTIVITIES, NATIONAL CONFERENCE OF CATHOLIC BISHOPS

Senator SPECTER. Our next witness is Mr. Richard Doerflinger, associate director for policy development for the secretariat for pro-life activities, National Conference of Catholic Bishops. During Mr. Doerflinger's 18 years of service he has been responsible for the preparation of policy statements and congressional testimony on a wide variety of subjects, including abortion, euthanasia, reproductive technologies, and other medical and moral issues for the Bishops Conference. Master of arts in divinity from the University of Chicago, widely published on ethical issues relating to the dignity of human life.

Thank you for joining us, Mr. Doerflinger, and the floor is yours.

Mr. DOERFLINGER. Thank you very much, Mr. Chairman.

I would ask that my longer statement be entered into the record and I will summarize it briefly.

Senator SPECTER. The full statement will be made a part of the record, as will all others, and you have the 5 minutes for summarizing or as you choose.

Mr. DOERFLINGER. I think it is important in assessing these experiments to know that when Congress decides to subsidize various forms of human experimentation it is making a moral and not just an economic decision. It is deciding that these are kinds of research that are sufficiently valuable and also sufficiently ethical to be done in the name of all Americans and all American taxpayers. By making those funding decisions, Government can make an important moral statement, set an example for private research, and help direct research toward avenues which are ethically appropriate as well as medically useful.

Three kinds of experiments involving human embryos have been discussed here. On one level, some of these experiments advance the debate on human cloning in ways that I think are interesting and productive, because they indicate that there are ways of making useful stem cells other than the use of human somatic cell nuclear transfer of cloning, and that in fact human cloning could be banned without endangering such research. There would be other avenues available.

At the same time, however, each of the experiments discussed raise ethical and, yes, legal questions of its own. Currently the drive for advances in fetal and embryonic research are balanced against ethical considerations in three different areas of law, the law on life fetal research which has been in existence since 1975, which treats the embryo and fetus, at least from the time of implantation, as a protectable human subject that must be protected from harmful research.

I say that with emphasis because a number of people here have talked about whether this kind of embryo or that is capable of creating a human being, and we saw pictures of little bouncing babies over here. But in the area of law we are talking about, a human being, a human subject worthy of protection, includes the human embryo.

There are also, of course, appropriations riders since 1995 which extend this to the pre-implantation human embryo, not only to special creation of embryos for research purposes, but also to harmful or destructive research on embryos already in existence.

Finally, we have fetal tissue transplantation guidelines which we, it will be no surprise to you, find inadequate because we do not think that tissues should be obtained from abortion victims at all. But those guidelines as well have some guidelines on how any use of tissue, even from a dead fetus, should be separated as much as possible from any decisions to destroy that fetus, that the destruction should not be geared toward the research or the timing and manner of it should not be geared toward the use of the tissue.

Along those lines, I find that two of the three experiments that have been discussed here are exactly the kind of thing that the human embryo research ban was directed against. Dr. West's experiment, with all due respect, does involve a use of cloning to create human embryos, which are then harvested for their stem cells and thus destroyed.

The fact is that the reason for using nuclear transfer here is to produce a genetic match for each individual patient. So for each individual patient who may need treatment, you would need to be making some number of new human embryos and then harvesting them for their tissues. This is a violation of both provisions of the current human embryo research ban. It creates embryos and then it destroys them.

The research from the University of Wisconsin also involves destroying embryos, though it does not involve creating them because it gets them from IVF clinics. Again, that violates the embryo research ban.

I think the more interesting question is whether subsequent use of the stem cells that have now been produced by that tissue would be violating the Federal ban. I think there we would have to look

for precedent to the current fetal tissue transplantation guidelines, which say that the tissue should not be used if the manner of the destruction of the original fetus or embryo was geared toward or related to the research. It has to be done for unrelated reasons. it cannot be linked with the research.

It seems to me that the way in which these cells are obtained, thus destroying the original embryo, is very much geared toward the banking of those tissues, and it raises an ethical problem that I think is parallel to the question that was already resolved by Congress with its guidelines on fetal tissue transplants.

Finally, in conclusion, I think it would be sad if Congress' attention were to focus chiefly on those avenues of research which garner front page news precisely because they are ethically problematic. Congress has an opportunity to use its funding power to advance medical research in ways that fully respect human life as well as promoting medical progress.

PREPARED STATEMENT

I believe that some of the aspects of Dr. Gearhart's research are very intriguing in this regard. We would like to explore it further, especially if the tissue that can be obtained can be obtained from sources other than abortion victims, because it does not seem, though there is some ambiguity here, that that research does not involve creating embryos which are then destroyed for cells.

Thank you very much for allowing me to testify.

Senator SPECTER. Mr. Doerflinger, we appreciate your being with us and thank you.

[The statement follows:]

PREPARED STATEMENT OF RICHARD M. DOERFLINGER

I am Richard M. Doerflinger, Associate Director for Policy Development at the Secretariat for Pro-Life Activities, National Conference of Catholic Bishops. I am grateful for the opportunity to present the Catholic bishops' ethical concerns regarding new developments in embryo research.

In discussions of human experimentation, the researcher's temptation is to think that if something technically can be done it ethically should be done—particularly if it may lead to medical benefits or advances in scientific knowledge. A civilized society will appreciate the possibilities opened up by research, but will insist that scientific progress must not come at the expense of human dignity. When this important balance is not maintained, abuses such as the Tuskegee syphilis study or the Cold War radiation experiments become a reality.

In deciding whether to subsidize various forms of human experimentation, legislators are not merely making an economic decision to allocate limited funds. On behalf of all citizens who pay taxes, they are making a moral decision. They are declaring that certain kinds of research are sufficiently valuable and ethically upright to be conducted in the name of all Americans—and that other kinds are not. By such funding decisions, government can make an important moral statement, set an example for private research, and help direct research toward avenues which fully respect human life and dignity as they seek to help humanity.

Three kinds of experiments involving human embryos or embryonic cells have recently come to public attention. On one level, some of these experiments advance the ethical and legal debate on human cloning. They indicate that cloning is not necessary for promising stem cell research, and thus that it may be banned without endangering such research. At the same time, however, each of these experiments raises ethical problems of its own.

Currently, the drive for advances in human fetal and embryonic research is balanced against ethical considerations in three significant areas of federal law. It is important to review these to address the question: What moral principles are reflected in these enactments that can help us to make a moral judgment on new experiments that may not have been anticipated before?

1. Live fetal research is governed by federal regulations on the protection of human subjects first issued in 1975 (now codified at 45 CFR § 46.101 et seq.). Federal regulations on fetal research treat the prenatal human being as a human subject worthy of protection, from the time of implantation in the womb (about one week after fertilization) until a child emerges from the womb and is found to be viable. Essentially the same standard is applied here as in regulations protecting live-born children: Since the unborn child is a helpless subject incapable of giving informed consent to experimentation, federally funded research involving this child is permissible only if (a) it could be therapeutic for that particular child (as with prenatal surgery to correct congenital defects), or (b) it is necessary to obtain important information and will not subject the child to significant risk of harm.[1] In 1985 Congress further clarified this standard through an amendment to the National Institutes of Health reauthorization act: In assessing research on live fetuses in utero, protection from risk must be "the same for fetuses which are intended to be aborted and fetuses which are intended to be carried to term" (42 USC § 289g). No matter what fate may be planned for the developing human being by others, the government must still make its own moral decision to respect life—it cannot single out certain lives as disposable, or as uniquely fit for harmful research, simply because someone else plans to show disrespect for those lives.

2. Embryo research involving human embryos outside the womb—such as embryos produced in the laboratory by *in vitro* fertilization (IVF) or cloning—has never received federal funding. Originally this was because the federal regulations of 1975 prevented funding of IVF experiments unless such experiments were deemed acceptable by an Ethics Advisory Board—and after the first such board produced inconclusive results in 1979, no Administration chose to appoint a new board. In 1994, after this regulation was rescinded by Congress, a Human Embryo Research Panel recommended to the National Institutes of Health that certain kinds of harmful non-therapeutic experiments on human embryos receive federal funding—but the Panel's recommendations were rejected in part by President Clinton, then rejected in their entirety by Congress. Since 1995, three successive Labor/HHS appropriations bills have prevented federal funding of experiments which involve (a) creating human embryos for research purposes, or (b) subjecting human embryos in the laboratory to risk of harm or death not permitted for fetuses in utero under the regulations on protecting human subjects. Since 1997 this rider has explicitly banned funding of experiments involving embryos produced by cloning using human body cells.[2]

3. Fetal tissue transplantation research has been a matter of extended controversy. Such research could receive federal funds during the Bush Administration only if the tissue was obtained from sources other than induced abortion. The possible use of ovaries from aborted fetuses to create research embryos provoked more controversy within the NIH Human Embryo Research Panel than perhaps any other proposal; in the end the Panel decided to defer any possible funding of such research until further discussion could take place. Under current federal funding policy, human fetal tissue—defined as "tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth," (42 U.S.C. § 289g–1(g))—may be used for "therapeutic purposes" only if various safeguards are followed to ensure that the researcher avoids participating in an abortion and has no effect on the "timing, method, or procedures used to terminate the pregnancy" (42 USC § 289g–1(b)(2)).

In our view, current safeguards on the use of fetal tissue are inadequate. The only sure way to prevent federally funded research from collaborating in and providing legitimacy for abortion is to forbid abortion as a source for potentially "therapeutic" tissue. Certainly, it would be wrong for Congress to apply to early human embryos any policy less protective than that now applied to the later embryo and fetus. Existing law explicitly applies to human embryos, and destroying or discarding an embryo in the laboratory is the moral equivalent of abortion. As Congress has already done in the case of live fetal research, it should make clear in this area of research that the same standards apply to human embryos whether inside or outside the womb.

Current law on live fetal and embryonic research is no mere political compromise. It is a reflection of universally accepted ethical principles governing experiments on

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[1] 45 CFR 46.208(a). Such research may only pose a "minimal risk," which means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 45 CFR § 46.102(i).

[2] The current funding ban is Section 511 of the Labor/HHS appropriations bill for fiscal year 1999, enacted as part of Public Law 105–277, the Omnibus Consolidated and Emergency Supplemental Appropriations Act for fiscal year 1999 (p. 399).

human subjects—principles reflected as well in the Nuremberg Code, the World Medical Association's Declaration of Helsinki and other statements. Members of the human species who cannot give informed consent for research should not be the subjects of an experiment unless they personally may benefit from it, or the experiment carries no significant risk of harming them. Only by such ethical principles do we prevent treating people as things—as mere means to obtaining knowledge or benefits for others.

Some will be surprised that such protections can exist under the U.S. Supreme Court's abortion decisions. But the Court has never said that government may not protect prenatal life outside the abortion context. It has even allowed states to declare that human life begins at conception, and that it deserves legal protection from that point onward—so long as this principle is not used to place an undue burden on a woman's "right" to choose abortion before viability.[3] Although states may not place meaningful restrictions or prohibitions on abortion under current Supreme Court jurisprudence, harmful experiments on human embryos are illegal in ten states regardless of how they are funded.[4] Public sentiment also seems even more opposed to public funding of such experiments than to funding of abortion.[5]

Moreover, a scientific consensus now recognizes the status of the early human embryo, and the continuity of human development from the one-celled stage onward, to a greater extent than was true even a few years ago. In the 1970s and 1980s, some embryologists spoke of the human embryo in its first week or two of development as a "pre-embryo" and claimed it deserved less respect than embryos of later stages. But most embryology textbooks have now dropped the term, and some texts openly refer to it as a "discarded" and "inaccurate" term.[6] The Human Embryo Research Panel and the National Bioethics Advisory Commission have both rejected the term; they describe the human embryo, including the one-celled zygote, as a living organism and "a developing form of human life."[7]

How is this human life treated in each of the three most recent developments in human embryo research?

UNIVERSITY OF WISCONSIN: STEM CELLS FROM AN IVF EMBRYO

The University of Wisconsin proposal seems to be exactly the kind of experiment that the federal funding ban was consciously directed against. Researchers obtained 36 live human embryos from IVF clinics, grew them to the blastocyst stage, and then destroyed them for their stem cells; cells from 14 of the embryos were placed in culture, and "cell clusters" from five were successfully cultured to grow tissue. The researchers report that the inner cells were "isolated by immunosurgery" from the rest of the embryo.[8] The effect is the same as if one were to "isolate" the heart and lungs from an adult human—the being from whom the cells are taken is killed.

This kind of experiment was recommended for federal funding in 1994 by the Human Embryo Research Panel, but rejected by Congress every year from 1995 to the present. In this respect it does not present a new issue, for Congress has already

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[3] *Webster* v. *Reproductive Health Services,* 492 U.S. 490 (1989).

[4] See testimony and documentation provided by Lori Andrews, J.D., to the NIH Human Embryo Research Panel, February 3, 1994. Ms. Andrews cites ten states whose laws on fetal research generally prohibit experiments on human embryos ex utero: Louisiana, Maine, Massachusetts, Michigan (which in 1997 also enacted a ban on creating human embryos by cloning), Minnesota, New Hampshire, North Dakota, Pennsylvania, Rhode Island and Utah.

[5] A national Tarrance poll in 1995 showed 18 percent support for using tax dollars for experiments that would involve destroying or discarding live human embryos in the first two weeks of development. Seventy-four percent of the Americans in the survey opposed such funding, with 64 percent strongly opposed. Press release, "Poll Shows Strong Opposition to Embryo Research Funding," United States Catholic Conference, July 25, 1995.

[6] See Ronan O'Rahilly and Fabiola Müller, "Human Embryology and Teratology," 2nd edition (New York: Wiley-Liss 1996) at 8, 12. Professor Lee Silver of Princeton University, a proponent of cloning and embryo research, recently declared that the term "pre-embryo" was embraced by IVF researchers "for reasons that are political, not scientific" in an effort to "allay moral concerns" about their research. Lee M. Silver, "Remaking Eden: Cloning and Beyond in a Brave New World" (New York: Avon Books 1997), 39.

[7] See: National Bioethics Advisory Commission, "Cloning Human Beings" (June 1997), appendix-2 ("embryo" as "the developing organism from the time of fertilization"); National Institutes of Health, "Report of the Human Embryo Research Panel" (September 1994), at 2 ("the preimplantation human embryo warrants serious moral consideration as a developing form of human life").

[8] James A. Thomson et al., "Embryonic Stem Cell Lines Derived from Human Blastocysts," 282 Science 1145–7 (6 November 1998) at 1147 n. 6.

decided that even so-called "spare" embryos from IVF clinics should not be subjected to destructive experiments using federal funds.[9]

Two new issues have been raised regarding this experiment, however.

First, could the embryonic cells that are removed from these human embryos, once isolated, be seen as human embryos themselves? The question arises because these inner cells are often described as the cells that would ultimately form the "embryo proper" as development continues. If removed from the original embryo but transferred to the nurturing environment of the womb, would each cell or each cluster of cells begin to develop as a new organism? Is a special environment provided by researchers to suppress such development and divert it toward undifferentiated growth as tissue instead? Certainly such diversion of embryonic development by use of molecular signals has been proposed by some researchers.[10] If that were at work here—if the experiment creates new embryos and then suppresses their development—funding such an experiment might also violate the current ban on creating human embryos for research purposes.

Second, what of the prospect of funding research that would use this tissue for supposedly therapeutic purposes after it has been grown in culture? Here, the ethical principles reflected in current law on fetal tissue argue against funding the research. One must refer here to the principles rather than to the exact letter of the law because, while it applies to embryos as well as fetuses, it speaks of induced abortion rather than of destroying embryos by dissection. But there seems to be no reason why the same ethical standard should not apply. Human embryos are destroyed precisely to obtain this tissue, and the timing and manner of the destruction are tailored to obtaining this kind of tissue. An effective separation between the destructive act and the harvesting of the tissue, which federal law requires in the case of tissue from an induced abortion, does not seem to exist here.

One positive development, however, is that this line of research has put to rest the claim made last year by some biotechnology companies that production of human embryos by cloning (somatic cell nuclear transfer) is necessary to develop therapies based on embryonic stem cells. Such claims assumed that adults could not be treated with such cells unless the embryos were produced by cloning to create a genetic "match" and avoid tissue rejection. But in his commentary on the Wisconsin experiment, John Gearhart has cited three other avenues, some of which were also cited by the National Bioethics Advisory Commission last year: Stem cells can be banked from multiple cell lines to prevent such reactions; they can be genetically altered to produce a universal donor line; or they can be customized using the relevant histocompatibility genes from the intended recipient.[11]

Whatever else may be said of this research, then, it means that proposed federal bans on human cloning need no longer be held hostage to the debate on stem cell research. But the experiment itself is unethical and should not be funded. Instead, as the National Bioethics Advisory Commission has already observed,[12] avenues should be explored for creating stem cell lines without creating or destroying human embryos.

JOHNS HOPKINS: STEM CELLS BASED ON PRIMORDIAL GERM CELLS FROM INDUCED ABORTION

Presumably the Johns Hopkins University study could not be funded unless it follows the provisions of current law regarding fetal tissue from induced abortions. We wish to reiterate here that we find the existing policy inadequate and would support federal funding only if the cells can be obtained from sources other than induced abortion.

The new question raised here is this: Are the primordial germ cells obtained from abortion victims being used to create human embryos, which are then destroyed or suppressed to provide tissue. Even the NIH Human Embryo Research Panel did not recommend funding such an experiment, and it would clearly be forbidden by the current embryo research ban.

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[9] On July 11, 1996, an amendment was offered by Rep. Nita Lowey (D–NY) to drop the ban on funding research involving "spare" embryos, while retaining the ban on special creation of "research embryos"; the amendment was defeated 256-to-167.

[10] See Lee M. Silver, *supra* note 6, at 128 (such molecular signals can be used as a way of "tricking" an early embryo into expanding as undifferentiated tissue, instead of undergoing normal growth and differentiation as an organism).

[11] John Gearhart, "New Potential for Human Embryonic Stem Cells," 282 Science 1061–2 (6 November 1998) at 1061.

[12] National Bioethics Advisory Commission, *supra* note 7, at 30–31. See NCCB Secretariat for Pro-Life Activities, "Would a Ban on Human Cloning Block Stem Cell Research?" (Fact sheet, 4/20/98; www.nccbuscc.org/prolife/issues/bioethic/fact498.htm).

There is some ambiguity in current reports of the new research, because the researchers speak of collecting "embryoid bodies" from these cultures and finding "derivatives of all three embryonic germ layers" in the culture. They add that some of these bodies form "complex structures closely resembling an embryo during early development," and that they "appear to recapitulate the normal developmental processes of early embryonic stages and promote the cell-cell interaction required for cell differentiation."[13]

However, if this research is now conducted—or could be conducted—to establish useful cell lines without creating early human embryos, it would avoid some of the serious ethical problems associated with other experiments in this field. In that case the only remaining ethical problem is the use of cells from induced abortion, which does not seem necessary to the nature of the research. We urge that the use of cells from spontaneous abortions, ectopic pregnancies or other sources be explored instead.[14]

ADVANCED CELL TECHNOLOGY: HUMAN CLONING USING COWS' EGGS

While this third type of experiment has not been fully reported in the medical literature it seems to pose a relatively new question—that of human/animal hybrids—as well as an old one, that of somatic cell nuclear transfer (cloning) to make human embryos for research purposes. Even the Human Embryo Research Panel opposed funding the former; the current ban on embryo research rightly forbids funding the latter.

The National Bioethics Advisory Commission, in its November 20 letter to President Clinton commenting on this experiment, rightly draws attention to the special ethical problems raised by combining human and animal cells to initiate embryonic development. On the one hand, this experiment does not create a hybrid in the sense of a being that is half human and half cow. All the nuclear genetic material comes from a human body cell; the cow egg contains some mitochondrial DNA, but this seems to be quickly taken over and directed by the human nucleus. On the other hand, proteins from the cow egg must be directing the remodeling of the chromosomes and thus the very earliest stages of development in this new being, and the ultimate effect of this is not known.

However, even if this experiment in one sense does not create a human/animal hybrid, it presents a new twist on the use of cloning to create human embryos for research purposes. Oddly, defenders of such an experiment must simultaneously argue that it is promising because it can produce genetically matched, fully human tissue for transplantation—and that it is not covered by the ban on embryo research because fusing a human nucleus and a cow egg does not really produce a human embryo.

Cows' eggs are apparently being used not to make hybrids as such, but to avoid one of the remaining practical obstacles to unlimited mass production of identical human embryos by cloning: the fact that human eggs are difficult to obtain in large numbers, and cannot be harvested in quantity without posing health dangers to women. Therefore this experiment not only poses ethical problems in its own right but could set the stage for further mistreatment of human life as an object of experimentation on a large scale. Funding for such an experiment should be, and is, banned by current law, which forbids creating a new organism from "one or more" human gametes or body cells by fertilization or cloning.

In its new letter the Commission seems very uncertain as to whether this experiment creates an embryo. But this is partly due to the Commission's own truncated approach to what constitutes an embryo. Its assumption seems to be that the new being is an embryo only if it can be proved capable of growing and developing into a new "human being," by which it means a live-born infant. But this is too narrow a standard. In many circumstances—especially those involving laboratory manipulation of new life—embryos are created in such a fatally damaged condition that they will not survive to live birth. This does not mean that they were never embryos. One might as well say that an infant born with a fatal disease, who will not survive to adulthood, was never an infant. This strange standard seems to grow out of the Commission's earlier attempts to propose that no "human cloning" has taken place so long as any human embryos created by cloning are ultimately discarded or abort-

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[13] Michael J. Shamblott, et al., "Derivation of pluripotent stem cells from cultured human primordial germ cells," *95 Proceedings of the National Academy of Sciences* 13726–13731 (November 1998) at 13726, 13729.

[14] See Peter J. Cataldo and Albert S. Moraczewski, O.P. (eds.), "The Fetal Tissue Issue: Medical and Ethical Aspects" (Braintree, MA: Pope John Center 1994).

ed instead of being implanted to attempt a live birth.[15] We believe the relevant question here is whether the new one-celled entity with a human nucleus begins, even for a brief time, to grow and develop as an early organism of the human species. If so, the experiment should be seen as involving the creation and destruction of human embryos and, as such, should not be funded.

Each of these new developments poses ethical questions, and none should be pursued by the federal government unless and until ethical questions have been satisfactorily answered.

A remaining question involves the other avenues for advancing stem cell research, or for advancing the medical goals to which this research is directed, without exploiting developing human beings. Last year, for example, we proposed to Congress that there may be nine promising alternatives to the use of cloning to provide stem cell lines—and eight of these seem to involve no use of embryonic stem cells at all.[16] In the same few weeks that these embryo experiments garnered such national attention, significant advances were reported in two of these areas: The use of growth factors to help hearts grow new replacement blood vessels, and the use of stem cells from placental blood to treat leukemia and other illnesses.[17]

It would be sad indeed if Congress's attention were to focus chiefly on those avenues of research which garner front-page news precisely because they are ethically problematic. Instead, Congress has an opportunity to use its funding power to channel medical research in ways which fully respect human life while advancing human progress. None of the new proposed experiments change in any way the ethical principle grounding current restrictions on human embryo research: In trying to serve humanity we should not support actions that are fundamentally wrong. Even a good end does not justify an evil means.

WOULD A BAN ON HUMAN CLONING BLOCK STEM CELL RESEARCH?

Some biotechnology companies claim that a ban on producing human embryos through cloning would stall important research in generating "stem cells" to cure a variety of diseases [Cong. Record, 2/5/98, S425]. To put this claim in perspective:

1. Cloning is desired as a source of "customized stem cell lines" which would be an exact genetic match to each individual patient with a given disease. But this would require each individual patient to undergo somatic cell nuclear transfer to produce one or many living human embryos who genetically are the patient's identical twin sisters or brothers. These embryos would then be destroyed to provide embryonic stem cells.

Two methods of obtaining the cells have been described. In one, the embryo is allowed to develop normally for a week or two to the blastocyst stage, at or after the usual time of implantation in the mother's womb; then this embryo, consisting of hundreds of cells, is dissected for its stem cells. The other method is to introduce molecular signals into the embryo's environment to "trick" its cells into departing from normal development and instead producing "a mass of undifferentiated tissue," which can then be reprogrammed into various kinds of cells [Lee Silver, "Remaking Eden: Cloning and Beyond in a Brave New World" (Avon Books 1997), p. 128]. In either case, the living embryo is destroyed.

2. This avenue for providing medical benefits has been described even by supporters as "largely conjectural" (J. Kassirer and N. Rosenthal, in "New England Journal of Medicine," March 26, 1998, p. 905). President Clinton's National Bioethics Advisory Commission called it "a rather expensive and far-fetched scenario." The Commission observed: "Because of ethical and moral concerns raised by the use of embryos for research purposes it would be far more desirable to explore the direct use of human cells of adult origin to produce specialized cells or tissues for transplantation into patients."

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[15] For a critique of this approach see Testimony of Cardinal William Keeler before the House Commerce Subcommittee on Health and Environment, February 12, 1998; reprinted in 27 Origins 597–601 (February 26, 1998).

[16] See NCCB Secretariat for Pro-Life Activities, *supra* note 12.

[17] See: "Gene Therapy Helps Mice Grow New Blood Vessels," Business Wire, November 20, 1998; "Injected Genes Help Grow Heart Bypasses," Washington Post, November 10, 1998 at A3; "Stem Cells 'Grow' in Value: Potential Benefits of Umbilical Cord Banking Further Validated," PRNewswire, November 27, 1998; Pablo Rubinstein et al., "Outcomes among 562 Recipients of Placental-Blood Transplants from Unrelated Donors," 339 New England Journal of Medicine 1565–77 (November 26, 1998); Robertson Parkman, "The Future of Placental-Blood Transplantation," 339 New England Journal of Medicine 1628–9 (November 26, 1998). In light of some researchers' zeal for use of cloning by nuclear transfer to ensure an exact genetic match between tissue and recipient, it is worth noting that placental blood transplants seem to be more effective in treating leukemia if they are not too close a genetic match. Rubinstein et al. at 1573.

The Commission outlined three alternative avenues for promising research using stem cells that do not involve human cloning, two of which do not use human embryos at all (“Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission,” June 1997, pp. 30–31).

THE COMMISSION'S ALTERNATIVES

The alternatives outlined by President Clinton's Commission are as follows:

1. Generating “a few, widely used and well characterized human embryonic stem cell lines, genetically altered to prevent graft rejection in all possible recipients.” This would raise its own ethical objections because it may involve producing and destroying some human embryos at the outset; but it does not require somatic cell nuclear transfer, or the creating and destroying of genetically related embryos for each individual patient.

2. Stimulating “proliferation and differentiation of the quiescent stem cells which are known to exist in many adult tissues, including even the nervous system.” Such stem cells could be “customized” to each individual patient and would not be from embryonic sources.

3. Identifying “methods by which somatic cells could be ‘de-differentiated’ and then ‘re-differentiated’ along a particular path.” This would permit “the growth of specialized cells compatible with a specific individual person for transplantation.” While at present this option is considered speculative, its feasibility is now enhanced by the central finding of the research that produced “Dolly” the sheep: An adult body cell can be “de-differentiated” surprisingly easily and regressed all the way back to a stage at which it can provide the nucleus for a new developing embryo. The question is: Can this regression be done to a point short of this, so an adult cell becomes the basis for cells that are like embryonic stem cells but never came from an embryo?

OTHER ALTERNATIVES (NOT EXPLICITLY CITED BY THE COMMISSION)

4. There are other promising sources of pluripotent (not embryonic) stem cells for treatment of disease. One example is hematopoietic (blood cell producing) stem cells from bone marrow or even from the umbilical cord blood in live births. These cells are already widely used in cancer treatment and in research on treating leukemia and other blood diseases. Their versatility was recently found to be even greater than once thought. For example, given the right environment bone marrow cells can be used to regenerate muscle tissue, opening up “a whole avenue of potential therapies that didn't exist before” for muscular dystrophies (“Bone Marrow Cells May Provide Muscle Power,” Science, 6 March 1998, p. 1456).

5. An enormously promising new source of stem cells is fetal bone marrow, which is “23 times more effective than adult marrow and eight times better than umbilical cord blood.” Recent studies show that “miscarriages can provide enough cells for transplantation if we would collect them effectively and store them in banking” (“Fetal marrow transplants promising against disease,” Detroit News, May 4, 1997). A stem cell line from such sources could provide a continuous supply of stem cells for research. It seems fetal bone marrow cells do not provoke the same immune reactions as adult or even newborn infant cells. This is true whether the unborn child is the donor or the recipient—that is, fetal cells can be used to treat adults, or adult bone marrow cells can be used to treat a child in the womb, without harmful immune reactions (see Jack Goldberg, “Fetal stem cell therapy,” in Jauniaux et al. (eds.) Embryonic Medicine and Therapy [Oxford U. Press 1997], pp. 474–80).

6. Other approaches to tissue regeneration involve the growth factors (activators and inhibitors of cell division and growth) responsible for the development of various cell types and tissues. These factors may be used to manipulate the cells of a tissue along the spectrum of differentiation, without the need to create stem cells first. Use of these factors has already shown promise in the clinical setting, as a vascular growth factor has been successful in saving the legs of three patients who had potentially lethal blood clots requiring amputation: Application of the growth factor allowed new vessels to grow around the clots and restore circulation to the legs (see Circulation, 3/31/97, pp. 1114 ff.). Now such factors have been used to generate new blood vessels to human hearts in 20 patients (“Drug Stimulates Growth of Heart Blood Vessels,” Washington Post Health, Feb. 24, 1998, p. 5).

7. Cells of different kinds are now being genetically engineered to repair damaged organs, especially by injecting them with an “oncogene” (a type of gene that causes cancer cells to reproduce rapidly). Heart cells produced with this gene can “survive and beat like normal heart muscle cells” when transferred to a damaged heart (“Study: Cells Repair Heart Damage,” Associated Press, March 17, 1998).

8. Methods are being developed for growing entire replacement organs, to treat children before or after birth. Cells of the needed variety are extracted from the child and cultured, then grown into organs in the laboratory using biodegradable scaffolds. The researchers say they hope to receive FDA approval for routine use of the technology within five years. They add that "there are no ethical concerns doing this treatment, as there are about some other procedures [such as human cloning]" ("Doctors grow animal organs," Washington Times, July 23, 1997, pp. A1, A18; also see Ben Bova, "Lost a lung? Grow your own," in USA Today, Feb. 24, 1998).

9. Promising avenues have been opened up in research on cancer and diseases of aging by studies of telomerase, dubbed by some "the immortality enzyme." It protects and rebuilds telomeres, the protective caps on the ends of chromosomes which deteriorate as we age. It is now believed that telomerase activity is required for the uncontrolled growth of most cancerous tumors. Mastering this enzyme may enable researchers to (a) inhibit its activity in cancer cells and reduce or stop tumor growth, and (b) to use telomerase itself in a controlled way to help rejuvenate and regenerate damaged tissues and organs. (J. Madeleine Nash, "The Immortality Enzyme," Time, Sept. 1, 1997).

In short: The claim that human embryo cloning is needed to advance promising medical research in cancer, degenerative diseases, etc. is simply false.

Even if the use of somatic cell nuclear transfer to create and cannibalize human embryos were to enable more rapid development of some limited branches of research (a proposition for which there is no firm evidence), the words of Professor Patricia King, co-chair of the NIH Human Embryo Research Panel, would remain valid:

The fertilization of human oocytes for research purposes is unnerving because human life is being created solely for human use * * *. In particular, the public should be assured that embryos will not be created because such creation is the most convenient means of answering important scientific questions that can be answered—perhaps more slowly—in other ways." [Final Report of the Human Embryo Research Panel (NIH, Sept. 27, 1994), p. 97].

STATEMENT OF THOMAS B. OKARMA, Ph.D., M.D., VICE PRESIDENT OF RESEARCH AND DEVELOPMENT, GERON CORP.

Senator SPECTER. We turn now to Dr. Thomas Okarma, Vice President of Research and Development of Geron Corporation. Since 1991 Dr. Okarma has served as a clinical associate professor of medicine at Stanford, authored over 100 publications, and has a dozen U.S. patents, a Ph.D., and M.D. from Stanford.

Thank you for joining us, Dr. Okarma, and the floor is yours.

Dr. OKARMA. Thank you for the invitation this morning.

We have heard ample testimony prior to my time validating the significance of the discoveries here, so I will not waste our time repeating those, and turn directly to why Geron chose to fund this research. Clearly, the therapeutic potential, as we have heard, is extraordinary. The potential, however, is realizable and portions of it can be reduced to practice based upon prior knowledge gained from animal stem cell work and the convergence of available complementary technologies developed by both the biotech industry and the academic community.

For example, Geron's demonstrated ability to use the telomerase gene to convey unlimited replicative capacity to differentiated cells is a key synergistic technology for developing the therapeutic applications we have been talking about today. Simply stated, as we learn to control the pathways that take stem cells down the road to neurons, blood vessels, and heart cells, we can immortalize them by telomerase gene transfer, so that sufficient quantities of these cells can be grown for transplant applications.

Geron's corporate mission is to develop treatments for chronic degenerative disease. These two technologies, telomerase gene transfer and human pluripotent stem cells, combine to make possible the

repair of degenerating organs with young, healthy, and fully functional cells.

Now, why the NIH should participate in the development of these applications. As we have heard, the scientific frontier opened up by the derivation of these cells is vast. However, industry will only explore that part of the frontier that may lead to products. Yet, much of this frontier is early basic research that would otherwise be underfunded by the private sector, thereby delaying and reducing the full impact of the discovery.

Basic mechanisms of early human cellular differentiation, intercellular communication, gene expression, and development biology are accessible to vigorous study for the first time. We must seize this opportunity and allow the most sophisticated biotechnology community in the world full access to these cells and appropriate levels of support to increase our understanding of the fundamental mechanisms that control our own development.

Last, I would like to summarize the position of Geron's ethics advisory board on the ethical justification of this kind of work. The company formed an ethics advisory board to advise us on the ethical issues associated with this research. The board, composed of medical ethicists of diverse religious traditions, carefully deliberated the issues and unanimously agreed that research on human pluripotent stem cells can be conducted ethically if performed within certain guidelines, which briefly are: treating the cells with appropriate respect due to early developmental tissue; obtaining full and informed consent from donors of the tissue; no reproductive cloning of human beings; accord for accepted norms of animal research; concern for global justice and the use of best efforts to develop and utilize the technology for all peoples; and last, participation by an independent ethics advisory board, in addition to an institutional review board, to assess the appropriateness of each research protocol.

Geron has and will continue to follow these guidelines. I have submitted the ethics board's report to this hearing and a full publication of these guidelines and their ethical foundations will be published by the board in conjunction with the Hastings Center.

PREPARED STATEMENT

In conclusion this morning, the therapeutic applications of this technology are real and near term. The benefits to society are clear, and their development appropriately falls under the purview of the National Institutes of Health. The ethical implications of the research, while requiring continual oversight as the technology matures, are nevertheless compelling today and argue strongly for the development and application of this technology for the improvement of health care.

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

[The statement follows:]

PREPARED STATEMENT OF THOMAS OKARMA

EXECUTIVE SUMMARY

First, I would like to thank the committee for inviting my testimony on behalf of Geron Corporation on the implications of human stem cell research. My comments will briefly cover (l) the significance of the discovery, (2) why Geron chose

to support this research, (3) why the NIH should participate in the development of biomedical applications of this research and (4) the view of Geron's Ethics Advisory Board on the ethical justification for research on the human pluripotent stem cell.

I respectfully request that my comments and submitted background materials be incorporated into the record of this hearing.

1. *The significance of the discovery*.—The human pluripotent stem cell has the potential to dramatically impact clinical medicine by introducing fundamentally new therapeutic technologies. No other human cell has the potential to (1) enable the development of cell and tissue transplantation therapies and gene therapy, (2) retool pharmaceutical research and development, and (3) accelerate research in human developmental biology, cellular differentiation mechanisms and cancer biology.

These cells are immortal in their undifferentiated state—they will grow indefinitely in culture, thereby providing a continuous source of homogeneous starting material for the production of uniform transplantable cells.

These cells are pluripotent, capable of forming all cells of the human body, making them a potential source of replacement cells for any failing organ. This would reduce the demand for organ donors, and more importantly, enable therapies to treat conditions that otherwise must be addressed by whole organ transplants such as:

—Heart muscle cells to restore the failing hearts of the five million Americans with congestive heart failure.

—Blood forming cells to provide hematologic support for the over one million new cases of invasive cancer in the US each year.

—Cells to line the inside of blood vessels to treat atherosclerosis which contributes to 650,000 deaths in the US each year.

—Insulin producing islet cells which could cure the 1.4 million US patients with Insulin Dependant Diabetes Mellitus.

—Nerve and brain cells for the one million Parkinson's disease patients, the 500,000 stroke victims or the four million Americans with Alzheimer's disease.

2. *Why Geron chose to fund this research*.—Clearly, the therapeutic potential is extraordinary. This potential is realizable and portions of it can be reduced to practice based upon prior knowledge gained from animal stem cell work, and the convergence of available complimentary technologies developed by both the biotechnology industry and the academic biomedical community. For example, Geron Corporation's demonstrated ability to use the telomerase gene to convey unlimited replicative capacity to differentiated cells is a key synergistic technology for developing therapeutic applications of human pluripotent stem cells. As we learn to control the pathways that take stem cells down the road to neurons, blood vessels, and heart cells, we can immortalize them by telomerase gene transfer so that sufficient quantities of these cells can be grown for transplant applications.

Geron's mission is to develop treatments for chronic, degenerative disease. These two technologies, telomerase gene transfer and human pluripotent stem cells, combine to make possible the repair of degenerating organs with young, healthy and fully functional cells.

3. *Why the NIH should participate in the development of biomedical applications of this research*.—The scientific frontier opened up by the derivation of human pluripotent stem cells is vast. Industry will only explore that part of the frontier that may lead to products. Yet much of this frontier is early, basic research that will be otherwise underfunded by the private sector, thereby delaying and reducing the full impact of this discovery. Basic mechanisms of early human cellular differentiation, intercellular communication, gene expression and developmental biology are accessible to vigorous study for the first time. We must seize this opportunity and allow the most sophisticated biomedical research community in the world full access to these cells and appropriate levels of support to increase our understanding of these fundamental mechanisms that control our own biological development.

4. *The position of Geron's Ethics Advisory Board on the ethical justification of research on human pluripotent stem cells*.—Geron formed an Ethics Advisory Board to advise the company on the ethical issues associated with this research. The board, composed of medical ethicists of diverse religious traditions, carefully deliberated the issues and unanimously agreed that research on human pluripotent stem cells can be conducted ethically if performed within certain guidelines:

(1) Treating the cells with respect appropriate to early developmental tissues. As stated by the Human Embryo Research Panel in their 1994 report, while deserving moral consideration due any human tissue, the early blastocyst (from which the stem cells are derived) does not warrant the same moral status as infants or children because of the absence of individuation and the lack of even the possibility of sentience and other qualities relevant to the moral status of persons. Therefore the

use of such cells for the purpose of saving or healing human life constitutes appropriate respect for these cells.

(2) Full and informed consent for tissue donation.

(3) No reproductive cloning of human beings or creation of chimeras (live animal combinations of two different species).

(4) Accord for accepted norms for animal research.

(5) Concern for global justice and the use of best efforts to develop and utilize the technology for all peoples.

(6) Participation by an independent ethics advisory board in addition to an Institutional Review Board to access the appropriateness of each research protocol.

Geron has and will continue to follow these guidelines. I have submitted the EAB's report to this hearing. A full publication on these guidelines and their ethical foundations will be published by the Board in conjunction with the Hastings Center.

In conclusion, the therapeutic applications of this technology are real and near term. The benefits to society are clear and their development appropriately falls under the purview of the NIH. The ethical implications of this research, while requiring continual oversight as the technology matures, are nevertheless compelling and argue strongly for the development and application of this technology for the improvement of health care.

THE FIRST DERIVATION OF HUMAN EMBRYONIC STEM CELLS

A Scientific Breakthrough for Transplantation Medicine, Pharmaceutical Research and Development, and Human Developmental Biology

The Breakthrough

Dr. James Thomson and colleagues at the University of Wisconsin, Madison, have for the first time successfully derived human embryonic stem cells (hES cells) and maintained them in tissue culture. Human embryonic stem cells are different from every other human stem cell previously isolated in that they have (i) an unlimited ability to divide and (ii) the capability to turn into any and all cell types and tissues in the body. These cells, licensed worldwide to Geron Corporation, hold great promise as a potentially universal source of replacement cells for transplantation and for use in screens for pharmaceutical research and development. Further, this promise is enhanced by Geron's cell immortalization technology which can potentially increase the lifespan of the differentiated cells produced from hES cells. The combined technology positions Geron to potentially supply an unlimited number of young cells and tissues for every organ in the body. In addition, hES cells will improve our understanding of reproductive and developmental biology. This could lead to better treatments for infertility and the discovery of new gene products to treat a wide variety of diseases.

Characteristics of Human Embrvonic Stem Cells

Derived from in vitro fertilized (IVF) blastocysts by a patentable laboratory process (US claim allowed) and donated under informed consent, hES cells have all the following characteristics which make them useful for multiple new therapeutic, pharmaceutical, and scientific applications.

1. *Pluripotency*.—hES cells can form virtually any cell in the body. Specifically they have the potential to form derivatives of all three cellular layers, including the gut epithelium (endoderrn); cartilage, bone, and smooth and striated muscle (mesoderm); and neural epithelium, embryonic ganglia and stratified squamous epithelium (ectoderm). Other later stage human stem cells have only a limited capability to form certain cell types such as blood cells (CD34+ stem cells) or connective tissue (mesenchymal stem cells).

2. *Self-renewing capacity*.—Under appropriate in vitro conditions, the hES cells repopulate themselves while remaining in the undifferentiated state. Therefore, they may be a continuous source of normal pluripotent human stem cells. We expect they can be scaled-up to commercial manufacturing levels for transplantation therapies. It has not been possible to maintain long term self-renewing capacity of other human stem cells in culture. The ability of hES cells to propagate indefinitely in the undifferentiated state without losing pluripotency is a characteristic that distinguishes them from all other "multipotent stem cells" discovered to date in humans. Among other benefits, the availability of scaled-up hES cell-derived cells and tissues for transplantation therapies could greatly reduce future reliance on primary human fetal and animal derived tissue.

3. *Telomerase expression*.—Telomerase is an RNA-dependent DNA polymerase demonstrated by Geron Corporation and its collaborators to be the enzyme which, when reactivated in normal cells, allows their continual proliferation. hES cells normally express the enzyme telomerase. The continual steady state activity of

telomerase in hES cells conveys replicative immortality. Other stem cells express telomerase at low levels or only periodically and therefore age and stop dividing with time.

4. *Normal chromosome structure (karyotvpe).*—hES cells maintain a structurally normal set of chromosomes (including the sex chromosomes, XX or XY) even after prolonged growth in vitro. They do not, for example, have any additions, deletions or rearrangements in their chromosomal structure as is characteristic of cell lines immortalized by viruses.

Because of these characteristics, hES cells are unique. No other cell has the potential of hES cells to (i) enable development of transplantation therapies, (ii) retool pharmaceutical research and development practices, and (iii) accelerate research in human developmental biology. Moreover, hES cells should provide an immediate, alternative source and industrial supply of starting material, relieving the need to continually resource primary human fetal-derived tissues. Much of the research necessary for product development work can be performed on the hES cells now made available by Dr. Thomson's breakthrough discovery. This research will be challenging and take time, yet holds vast biomedical and therapeutic potential. Geron Corporation has provided funding and support for Dr. Thompson's work and holds worldwide rights to his discovery.

Benefits to Science and Medicine

The derivation of hES cells is a fundamental discovery that holds promise for three major areas of biomedicine: (1) Transplantation medicine, (2) Pharmaceutical research and development and (3) Human developmental biology.

1. *Transplantation Medicine.*—The potential therapeutic impact of hES cells in transplantation medicine is enormous because of their expected capability to produce virtually unlimited quantities of any cell in the body. In addition, they have the potential to be genetically engineered to prevent their immune rejection by the transplant recipient. Examples of medically relevant cells that could be developed and tested for transplantation therapies in humans include the following:

(i) *Cardiomyocytes.*—Heart muscle cells do not proliferate during adult life. When heart muscle is damaged by injury or ischemia, functional heart muscle is replaced with non-functional scar tissue. Congestive heart failure, a common consequence of heart muscle or valve damage, affects nearly 5 million people in the United States, with 400,000 new cases diagnosed each year. In addition, about 1.5 million people each year suffer myocardial infarction, the primary cause of heart muscle damage, and about one third of them die.

Mouse cardiomyocytes derived from mouse embryonic stem cells have been prepared and injected into the hearts of recipient adult mice. The injected cardiomyoctes repopulated the myocardial tissue and stably integrated with host myocardial tissue (Klug, et al., 1996, J Clin Invest 98:216–224). These results suggest that the development of hES cell-derived cardiomyocytes for cellular transplantation therapy of congestive heart failure and myocardial infarction in humans is technically feasible.

(ii) *Hematopoietic stem cells.*—Bone marrow transplantation is a life saving procedure used in pediatric and adult cancers. In 1995, there were approximately 4,500 allogeneic (donor) and 8,000 autologous (self) blood and bone marrow transplants performed in North America. The number of procedures performed dramatically under-serves the medical need. The main factor which limits the number of procedures is tissue or donor availability.

Blood-forming stem cells could be developed from hES cells as has been done using mouse embryonic stem cells (Kennedy, et al., 1997, Nature 386:488–492). This would increase the availability of these cells and reduce reliance on donors. Further, hES cell-derived hematopoietic stem cells potentially could be genetically engineered to resist infection by such agents as the HIV virus and used in a transplant setting for the treatment of AIDS, or possibly used for the treatment of patients with sickle cell anemia.

(iii) *Endothelial cells.*—(blood vessel forming cells). Endothelial cells have been observed in hES-derived teratomas in mice and mouse endothelial cells have been derived from mouse ES cells (Vittet, et al., 1996 Blood 88:3424-3431). These blood vessel forming cells could be generated from hES cells and used to re-line blood vessels for the purpose of treating atherosclerosis, a condition which contributes to over 650,000 deaths annually in the US. hES-derived endothelial cells could also be used for generating new blood vessels in ischemic regions of the heart, brain, or lower extremities to treat angina, stroke and arterial insufficiency.

(iv) *Islet cells.*—The 1.4 million U.S. patients with Insulin Dependant Diabetes Mellitus potentially could be treated with islet cells derived from hES cells and iso-

lated for this use. Such human cells are unavailable today and could provide a lifelong cure for this disease.

(v) *Neurons.*—It has been demonstrated that mouse neurons can be derived from mouse embryonic stem cells (Bain, et al., 1995, Dev Biol 168:342-357). Neurons derived from hES cells potentially could be prepared for the treatment of (i) the over 1 million individuals in the United States who suffer from Parkinson's disease, (ii) the 500,000 U.S. citizens who suffer a stroke each year, and (iii) even Alzheimer's disease, which now affects over four million Americans.

(vi) *Fibroblast and keratinocyte skin cells.*—of mice have been observed in cultures of differentiated mouse ES cells (Bagutti, et al., 1996, Dev Biol 179:184–196). We expect that comparable human skin cells could be produced from hES cells and used for wound healing and the treatment of burns.

(vii) *Chondrocytes.*—cartilage forming cells, also observed in hES-derived teratomas in mice, could potentially be generated from hES cells for cartilage replacement in osteoarthritis which affects over 16 million Americans, or rheumatoid arthritis which affects over two million persons in the United States.

2. *Pharmaceutical research and development.*— The potential to produce and supply unlimited quantities of normal human cells of virtually any tissue type could have a major impact on pharmaceutical research and development. Until now, the only cell lines available for this work were either animal in origin or abnormal transformed human cells. Permanent, stable sources for normal human differentiated cells may be developed for drug screening and testing, drug toxicology studies, as well as new drug target identification. Further, because hES cells express telomerase and can therefore undergo multiple rounds of a sophisticated type of genetic engineering called gene targeting, cellular models of human disease could be developed for use in drug development. Finally, cell lines derived from hES cells may be useful for developing screens for teratogens (drugs causing birth defects), extending the capability of current assays based on bacterial and murine systems.

3. *Human reproductive and developmental biology.*—Unraveling the biology of hES cells as they differentiate into functional cell types in vitro offers a unique platform to understand and harness nature's mechanisms of embryonic development, tissue differentiation and repair. Such understanding has potential for contributing to (i) the treatment of fertility disorders which affect one out of every six couples in the U.S. trying to become pregnant, (ii) the prevention of premature pregnancy loss, estimated to be 15 percent of recognized pregnancies in the US, and (iii) the diagnosis and prevention of birth defects which afflict 3 percent of live births in the US.

Until now, the early developmental events which naturally occur during human embryogenesis have been inaccessible to direct study. The availability of hES cells may facilitate a molecular understanding of how specific human tissues and organs develop without conducting research on human embryos or fetuses. Further, it is possible that novel genes which fundamentally control tissue differentiation could be identified by the application of genomic technologies to cultured hES cells as they differentiate into a variety of functional cell types. These new gene products may have potential to be developed into therapeutic proteins with possible applications including wound healing, stroke, myocardial infarction, spinal cord injury, and tissue regeneration.

These potential clinical applications would utilize suspensions of hES cell-derived differentiated cells administered by injection. With further technical development, complex multi-cellular solid tissues and organs potentially could be developed for application in organ support therapies for lung, kidney, liver, cardiac and brain diseases. While the biomedical and therapeutic promise of hES cells is vast, it should be emphasized again that the additional research and development required to realize this potential is significant.

This Breakthrough is Enhanced by Geron's Technology

Geron's focus is on identifying and modifying for therapeutic purposes the molecular mechanisms that control cellular aging and replication. The company and its collaborators have cloned the enzyme telomerase which extends the replicative capacity of cells. The application of telomerase gene transfer technology to hES cells is part of Geron's ongoing work in cell and gene therapy and flows from its published results on extending cellular replicative potential as reported in Science earlier this year (Bodnar, et al., 1998, Science 349–352). Telomerase activity is quickly down-regulated after hES cells differentiate. The ability to reactivate telomerase in differentiated cells derived from hES cells could prolong their replicative lifespan indefinitely and thereby make them the preferred cells for applications in transplantation medicine because they should be long-lived and form a durable graft.

The History of hES Cell Derivation

Work to derive and maintain undifferentiated pluripotent cell lines dates back to the 1960s with the demonstration that certain cancer-derived mouse cells were capable of forming multiple tissue types. These cancerous cells proved to be of limited research utility, and efforts continued to derive non-cancerous, self-renewing, pluripotent stem cells from mouse embryos. Eventually, the successful derivation of murine embryonic stem cells from the inner cell mass of mouse blastocysts in 1981 allowed culture conditions to be defined that supported their unlimited propagation. These cells were soon shown to be totipotent and capable of contributing to the germ line in mice (passed on from generation to generation). The use of murine embryonic stem cells in gene targeting experiments has resulted in development of numerous mouse models of human disease (knock-out mice) and has provided valuable insights into developmental biology, much of which has been applied to human medicine. However, these experiments also demonstrated that there are major differences in developmental biology between mice and humans. These fundamental differences formed a rationale to pursue the derivation of embryonic stem cells from higher mammals.

Methods developed for deriving mouse embryonic stem cells were applied toward deriving embryonic stem cell lines from other animals such as sheep (1987), hamster (1988), pig (1990), and rabbit (1993). The first non-human primate embryonic stem cell was described by Dr. James Thomson at the University of Wisconsin, Madison in 1995. The derivation process for primate embryonic stem cells differed from methods developed for the mouse and other non-primate species. Furthermore, there are differences between primate ES cells and other ES cells. For example, currently, primate embyonic stem cells have a absolute requirement for feeder layers of irradiated fibroblasts in order to propagate in the undifferentiated state in vitro. They also differ from mouse ES cells in colony appearance and biochemical surface markers.

Like other mammalian embryonic stem cells, however, primate embryonic stem cells differentiate and form tissues of all three cellular layers when injected into immunodeficient mice, proving their pluripotency. Published reports show that these primate embryonic stem cells have been maintained in culture for more than a year, during which time they have retained their pluripotency, self-renewing capacity, and their normal karyotype (Thomson, et al., (1995), PNAS 92:7844–7848).

Dr. Thomson subsequently applied his primate embryonic stem cell derivation technology to voluntarily donated in vitro fertilized human blastocysts. He now reports the first successful derivation and propagation of human embryonic stem cells which, like the primate embryonic stem cells derived earlier, are pluripotent,[1] self renewing, and telomerase positive with a normal karyotype (Thomson, et al., (1998) Science, in press).

The Derivation of Human Embryonic Stem Cells

In vitro fertilized preimplantation stage blastocysts, produced initially but not used for clinical purposes, were donated voluntarily with conformed consent, by clients undergoing in vitro fertilization procedures. The derivation protocols were approved by the University of Wisconsin Institutional Review Board. After culturing to the blastocyst stage, the inner cell masses were recovered and cultured on irradiated mouse embryonic fibroblast feeder layers. After about two weeks in culture, the hES cells were dissociated and replated on fresh feeder layers. The hES cells were thereafter maintained for months in the undifferentiated state by serially sub-culturing onto fresh, irradiated mouse embryonic fibroblast feeder layers (Fig 1).

The Demonstration of Pluripotency

The capability of hES cells to differentiate into virtually any cell in the body was demonstrated by experiments in which the hES cells were injected into severe combined immunodeficient (scid) mice. Each of the injected cell lines produced non-malignant tissue masses (teratomas) that contained a wide range of human differentiated cells and tissues, including gut epithelium (endoderm); cartilage, bone, smooth and striated muscle (mesoderm); and neural epithelium, embryonic ganglia and stratified squamous epithelium (ectoderm). These three cellular layers (endoderm, mesoderm and ectoderm) have the potential to form all the cells in the body (Fig 2).

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[1] hES cells are referred to as pluripotent. All non-human ES cells are referred to as totipotent (capable of developing into the whole organism). The only way to prove totipotency is to derive an organism from the cell. This has been done with animal ES cells but will not be done with hES cells for ethical reasons.

The Significance of Telomerase Expression in hES Cells

In general, cells that express telomerase have the ability to divide indefinitely. Cells not expressing telomerase (most cells of the body) have a limited replicative capacity. hES cells express telomerase and therefore have infinite replicative capacity.

Telomerase is an enzyme, cloned by Geron and collaborators, that maintains the length of the telomeric regions (ends) of chromosomes and thereby prevents cell senescence. In fact, telomerase expression is highly correlated with replicative immortality in certain human cells. Similarly, re-introduction of telomerase by gene transfer into normal telomerase-negative cells confers replicative immortality (Bodnar, et al., 1998, Science 349–352). Telomerase activity is continuously present in adult male reproductive tissue and is present in human fetal heart, liver, and kidney cells but only for the first 11–15 weeks of embryonic development.

The benefits of telomerase expression in hES cells are twofold. First, the cells are immortal, enabling the production of an unlimited supply of undifferentiated pluripotent cells. Second, the cells are amenable to a sophisticated type of genetic engineering called gene targeting which allows the insertion of new genes to specific sites on the chromosome to enhance their expression and control.

Geron's Intellectual Property Position in hES Cells

Geron's intellectual property estate in the embryonic stem cell field consists of:

1. A worldwide license to the stem cell patent estate of Dr. James Thomson and the Wisconsin Alumni Research Foundation. Licensed patent applications include primate and human embryonic stem cells and related diagnostic and therapeutic products. A broad claim has already been allowed in the US from this estate covering primate embryonic stem cells with the characteristics described in the Thomson Science paper just published.
2. A worldwide license to the stem cell patent estate of Dr. John Gearhart and the Johns Hopkins University. This license includes all applications of human embryonic stem cells including diagnostic and therapeutic products.
3. A worldwide license to patent applications of Dr. Roger Pedersen and the Regents of the University of California covering diagnostic and therapeutic products based on hES cells.
4. A license of the Genpharm patents on genetic modification of human and primate embryonic stem cells by homologous recombination (gene targeting). This estate consists of four issued US patents and eight pending US patent applications.
5. Geron-owned patent applications including screens for hES cell growth factors, media formulation and preferred growth conditions, and also relating to telomerase gene transfer and recombinant telomerase expression in embryonic stem cells and their derivatives.

The Ethical Considerations in hES Cell Product Development

These hES cells are derived from in vitro fertilized blastocysts. IVF clinic patients voluntarily donated the blastocysts with informed consent. The University of Wisconsin-Madison Institutional Review Board approved all of the research protocols. Geron's intended hES cell research as well as that of its collaborators is conducted within the suggested guidelines of the 1994 report by the NIH Human Embryo Research Panel.

Human embryonic stem cells are obtained from in vitro fertilized human blastocysts and capable of differentiating into virtually any cell in the body. However, hES cells are derived from the blastocyst inner cell mass by a laboratory process and are not the cellular equivalent of an embryo.

The small cluster of cells (inner cell mass) within the in vitro fertilized blastocyst from which the hES cells are derived have not yet differentiated and are unspecialized. The inner cell mass does not form discrete parts of an individual embryo as one or more of these inner mass cells can be removed from the blastocyst (for preimplantation diagnosis) without affecting subsequent fetal development after transfer to the uterus. If hES cells were to be transferred to a uterus, the hES cells would not form an embryo because other cells necessary for implantation and embryogenesis have been lost in the derivation process.

Geron has adopted the conclusion of the NIH Human Embryo Research Panel in its 1994 report. The cells will not be used for (i) cloning humans, (ii) transfering to a uterus, or (iii) generating human-human or human-animal chimeras (live animal hybrids produced by mixing embryonic stem cells of different individuals or species).

Geron has formed an independent Ethics Advisory Board composed of prominent bioethicists to advise the company on the ethical implications of hES cell product development strategies. The Board has unanimously agreed that research on hES

cells can be conducted ethically if performed within the guidelines adopted by Geron Corporation and its collaborators. To complement its internal research and development, Geron Corporation maintains sponsored research collaborations with Dr. James Thomson, Dr. John Gearhart and Dr. Roger Pedersen, nationally prominent investigators in human stem cell research whose protocols have all been reviewed and approved by their respective Institutional Review Boards.

The Next Steps in hES Cell Research and Development

Now that the major bottleneck in developing hES cell-derived cells and tissue for transplantation has been eliminated with the derivation of hES cells, Geron plans to develop other supporting technologies including:

(i) *Human embryonic stem cell production, scale up and genetic engineering*.—A standardized process will need to be developed for large-scale production of hES cell-derived differentiated cells for transplantation. Quality control criteria will need to be developed for the feeder lines, culture media, growth factors, sterility assays and phenotypic markers used for the clinical production of hES cells. Protocols will need to be developed and optimized for genetically engineered hES cells. Techniques of gene targeting [2] (homologous recombination) will need to be optimized.

(ii) *Differentiation control*.—Technologies using tissue-specific promoters and drug selection strategies will need to be developed to direct the differentiation of these cells towards the desired final cell and tissue product. Other methods of cell purification such as cell sorting will also need to be explored. Factors useful to drive cells toward specific differentiation states will need to be identified and used in conjunction with drug selection-enrichment technologies. Techniques will need to be developed to prevent the rejection of hES cell derived tissues by transplant recipients.

(iii) *Primate model development*.—Human therapeutic products derived from hES cells will require in vitro and animal testing. With Geron's license to the non-human primate embryonic stem cells of monkeys (also identified by Dr. Thomson at the University of Wisconsin-Madison), Geron has the capability to develop and test its proposed therapeutic products in a highly useful primate model.

This continuing research and development activity will constitute Geron Corporation's hES cell technology development program. Geron has work plans in place with Drs. Thomson, Gearhart and Pedersen, and will seek to collaborate with other academic centers and biotechnology and pharmaceutical companies in developing these therapeutic opportunities.

The availability of pluripotent, self-renewing hES cells that can be differentiated into bulk-manufactured, functional, youthful cells and tissues will potentially usher in a new era of therapeutic opportunities in transplantation medicine, pharmaceutical research and development, and developmental biology that could positively impact many millions of patients worldwide.

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[2] Gene targeting is a sophisticated technique of genetic engineering which allows the gene of interest to be "targeted to" a specific and desired location in the chromosome, thereby allowing the gene of interest to be controlled by the normal regulators of that gene's expression. Because gene targeting requires several rounds of selection, each requiring multiple cycles of cell division, only immortalized cells have sufficient replicative capacity to be suitable for this form of genetic engineering.

GERON CORPORATION

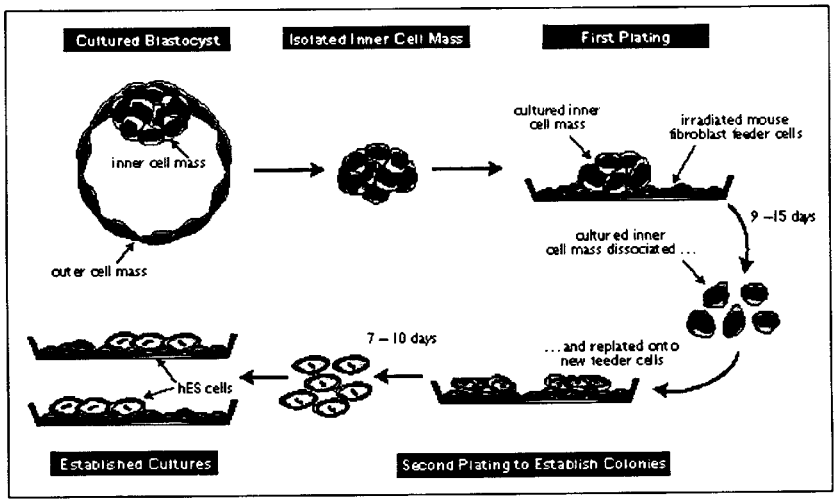

Figure 1

Derivation of hES Cells

Graphic depicts derivation of hES cells from the inner cell mass of a cultured blastocyst to establish stable hES cell lines in culture dishes.

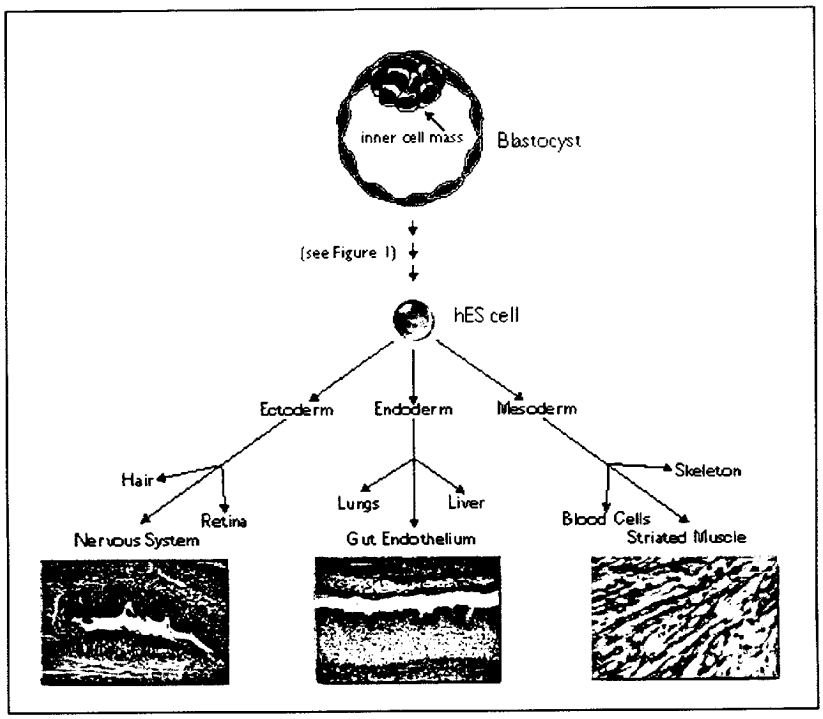

Figure 2

Differentiation of hES Cells into Three Germ Layers

Graphic depicts the potential for hES cells (derived from the inner cell mass of the blastocyst) to differentiate into any and all cell types and tissues in the body. Photomicrographs of actual human differentiated tissue containing nerve (ectoderm), gut (endoderm), and striated muscle (mesoderm) tissue which illustrate examples of all three tissue layers resulting from hES cell differentiation.

GLOSSARY

First Derivation of Human Embryonic Stem Cells

Allogeneic: When describing transplantation biology, the donating individual is of the same species, but not one's self.

Angina: A condition with severe and constricting pain, usually referring to the heart.

Autologous: When describing transplantation biology, the donating individual is one's self.

Blastocyst: In mammalian embryology, the preimplantation embryo consisting of a sphere of cells with an outer cell layer, a fluid-filled cavity, and a cluster of cells on the interior that is the inner cell mass.

Cardiomyocytes: Mature, differentiated heart muscle cells.

Chondrocytes: Mature, differentiated cartilage cells chromosomes: Composed chiefly of DNA, they are the carrier of genes, the hereditary information.

Cloning: A term that is applied to genes, cells or entire organisms that are derived from, and are genetically identical to, a single common ancestor gene, cell, or organism, respectively.

Differentiate: To undergo a cellular progression to a more specialized type.

Embryo (human): An organism at its earliest stage of development which has the potential, if transferred to a uterus, to develop in the normal course of events into a living human being.

Embryogenesis: The process of embryo formation.

Feeder layers of irradiated mouse fibroblasts: mouse cells which have been treated to prevent their division, but which produce important growth factors allowing ES cells to repopulate.

Fibroblast cells: Cells that give rise to connective tissue.

Keratinocytes: Cells that synthesize keratin as in the skin, hair, and nails.

Gene targeting: The insertion of DNA into specific sites or genes within the genome of selected cells to alter gene expression for therapeutic applications.

Genome: The genetic material (complete set of chromosomes) of an organism.

Genomic technology: Sequencing genes and their expression products.

Hematopoietic: Pertaining to the formation of blood cells.

hES cells: Human embryonic stem cells, they are immortal (self-renewing), telomerase positive, and pluripotent.

Homologous recombination: A process whereby a specific gene sequence within the genome is replaced with a related gene sequence using the cellular recombination enzymes.

Inner cell mass: The cluster of cells within the blastocyst from which hES cells are derived.

Implantation: Attachment of a blastocyst to the endometrium.

In vitro: Performed in an artificial environment such as a test tube.

In vivo: Performed in a living organism.

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

Ischemia: Deficiency of oxygen in a tissue due to obstruction of a blood vessel.

Islet cells: Cells of the pancreas that produce and secrete insulin; degeneration of islet cells is the cause of Insulin Dependent Diabetes Mellitus.

Karyotype: The chromosomal characteristics of a cell.

Knock-out mice: Mice that have had one or both copies of a specific gene deleted or inactivated Page Three/First Derivation of Human Embryonic Stem Cells.

Murine: Of or relating to the rodent family.

Myocardial infarction: Heart attack.

Pluripotent: The ability to develop into multiple cell types including all three embryonic lineages forming the body organs, nervous system, skin, muscle, and skeleton.

Severe combined imunodeficient (scid) mice: Mice with the majority of their immune defenses not functioning.

Telomerase: An enzyme composed of a protein and an RNA template which synthesizes telomeric DNA at the ends of chromosomes and confers replicative immortality to cells.

Telomeres: The ends of chromosomes.

Teratoma: A non-malignant tumor consisting of different types of tissue caused by the growth of embryonic stem cells at an abnormal site in the body.

Totipotent: The ability of a cell to give rise to all cells and tissues in the body including the reproductive organs.

Undifferentiated: Having no limited or specialized function or structure, as in stem cells.

Zygote: Cell formed by union of two gametes—male and female germ cells.

Questions and Answers

Science/Technical

Question. What is the relationship between human ES cells and other human stem cells?

Answer. First, under appropriate in vitro conditions, hES cells repopulate themselves while remaining in the undifferentiated state. They are, therefore, a potentially continuous source of pluripotent human stem cells which could be developed to generate specific cells or tissues and scaled-up to commercial manufacturing levels for transplantation therapies. It has not been possible to maintain in vitro long term self-renewing capacity in the undifferentiated state with any other human stem cell. The ability of hES cells to propagate indefinitely in the undifferentiated

state without losing pluripotency is one of the characteristics that distinguishes them from all other stem cells discovered to date in humans.

Second, other human stem cells have only a limited capacity to form differentiated cell or tissue types such as blood cells (CD34+ stem cells) or connective tissues (mesenchymal stem cells). hES cells, in contrast, have the unique capability to form any and all cell and tissue types in the body.

Question. Could these cells be used to grow entire organs?

Answer. Human Embryonic Stem cells form differentiated tissues with organ-like features when injected into immuno-compromised mice. Under appropriate laboratory conditions and with the development of supportive technologies, it may be possible to grow multicellular tissues and perhaps whole organs in a laboratory environment for subsequent therapeutic applications in humans.

Question Will additional hES cells be derived?

Answer. Although much of the basic research and developmental work required to translate this discovery into products of medical value can be performed on the hES lines already isolated by Dr. Thomson, other hES lines will be isolated to support product development. Because the cells are believed to be immortal and pluripotent, and are amenable to sophisticated forms of genetic engineering, we envision the possibility of producing multiple types of transplantable tissues from single hES lines, reducing the necessity to routinely generate new ES cell lines for each application.

Question. How does this technology relate to cloning human beings?

Answer. As has been documented with animals, the basic technology required to clone mammals is already available, although not at this point reduced to reliable practice. Dolly was one success in 278 attempts. To our knowledge, Dolly and all other animals cloned to date, were cloned using nuclear transfer procedures which utilize adult cell nuclei and enucleated egg cell cytoplasm, not embryonic stem cells. Using nuclear transfer procedures, it might be possible in the future to clone human beings, without use of hES cell technology.

However, Geron fully supports the current ban in the State of California on cloning human beings for reasons outlined in the 1997 report of the National Bioethics Advisory Commission on human cloning.

Medical Potential

Question. What are the hurdles to developing therapeutic applications of this technology—for example, growing heart muscle cells for heart disease patients?

Answer. Many lessons have been learned from animal experiments with heart muscle, nerve and certain blood cells. For example, heart muscle cells have been derived from mouse embryonic stem cells and have been injected into hearts of adult mice where they were shown to functionally integrate into the heart muscle. In order to accomplish this, the mouse embryonic stem cells were genetically modified using procedures that allowed the selection of only cardiomyocytes from the differentiating cultures. These genetically-based differentiation technologies will need to be tested in primate and hES cells in an attempt to produce cardiomyocytes of sufficient purity.

Question. How long will it take before you begin any human clinical trials using this technology?

Answer. Many technologies will need to be developed to realize the full potential of the clinical applications of hES cells. Furthermore, these applications, once developed, will need to be tested in primate models. It is therefore difficult to predict how soon human clinical trials using this technology could begin.

Question. Would it be easier—and just as effective—to work with stem cells further downstream, that have already differentiated into specific cell types?

Answer. There are several approaches now in human clinical trials that utilize mature, multipotent stem cells (blood-forming cells, neuron-forming cells and cartilage-forming cells). These human trials will provide valuable insights toward the use of stem cells in transplantation procedures. However, each of these approaches requires that an individual donor (or the patient) be used as the source of the cells which are then subsequently processed in a laboratory and transplanted. These procedures, necessary to address tissue sourcing constraints and immune system rejection, are costly, time consuming, and inefficient. These downstream stem cells have already differentiated and are therefore more difficult to modify to make them tissue compatible.

Telomerase positive hES cells, on the other hand, are believed to be self-renewing and therefore scalable. One culture line can produce many different tissues thereby improving production efficiency. We also believe that hES cells, because they are more primitive and developmentally upstream, could be more likely to develop into fully functional integrated tissues once transplanted. Further, these hES cells poten-

tially can undergo multiple rounds of sophisticated genetic engineering to become tissue compatible, thereby eliminating the need to identify compatible donors as a source of the cells.

Business Issues

Question. How is Geron involved in this breakthrough?

Answer. We have funded Dr. Thomson's research for three years and collaborated with his lab on the characterization of the hES cells he derived. Geron also has a worldwide license to this discovery.

Question. What evidence is there to support that there will be any viable commercial uses based on this discovery?

Answer. Several of the proposed hES cell-based therapeutic applications have already been demonstrated in mice with murine ES cells. Geron believes it is likely that these technologies will be transferable with appropriate modifications. We believe that results achieved in animals potentially can be extended and developed into viable therapeutic strategies for humans.

Furthermore, there are commercial applications of hES technology that could be reduced to practice before the cells become available for tissue transplantation. We expect to collaborate with one or more genomics companies to identify novel genes that could be used to generate therapeutic proteins to help regenerate tissue in such conditions as spinal cord injury, stroke, or heart attacks.

Also, cells derived from hES cells may also be commercialized as a technology for use in drug screening, drug target identification or even identifying teratogens (drugs that cause fetal abnormalities) and therefore make the pharmaceutical research and development process more efficient.

Question. What will Geron's sustainable advantage be in competing with other stem cell companies?

Answer. Human embryonic stem cell technology fits in extremely well with Geron's telomere and telomerase technology platform. Geron and its collaborators have cloned the telomerase enzyme and demonstrated its utility in immortalizing cells for potential therapeutic applications. Telomerase gene transfer technology, being developed by Geron, could be important for the development of compatible, transplantable tissues derived from hES cells that result in durable, long lasting grafts. Further, hES cells are the earliest, most upstream pluripotential stem cells and the only human stem cell thus far shown to self-renew in the undifferentiated state. These characteristics provide unique capabilities to these cells which, we believe, will likely translate into technical and commercial competitive advantages.

Question. What about differentiated stem cells: are there issued or pending patents on these later-stage cells by other companies or institutions?

Answer. There are issued patents and pending patent applications on later stage differentiated stem cells and non-primate embryonic stem cells held by other companies or institutions. It is possible that Geron may determine it advantageous to negotiate a license certain of these technologies. However, the human embryonic stem cell occurs developmentally upstream from all other stem cells and a broad claim covering these cells has already been allowed by the US patent office. Importantly, we will also attempt to patent genetically engineered downstream cells derived from hES cells. Geron will continue to aggressively pursue worldwide protection for this technology and subsequent related inventions.

Question. What about growth and differentiation factors: does Geron need to license this technology?

Answer. Geron may need to in-license certain technologies to enable the development of the full therapeutic potential of hES cells, including certain vector technologies, genetic differentiation technologies, and growth factors. We will attempt to accomplish this via licensing agreements and other forms of partnerships.

Question. Isn't there a business risk that work in this field will someday be prohibited by the government?

Answer. Geron Corporation believes that the potential benefits to medicine we have described are enormously important. Geron, and the scientific and medical communities, generally support appropriate scientific and ethical guidelines for conducting research in the field. All product applications will, as is the case for all new therapeutics, be carefully evaluated by the FDA. We anticipate that follow-on research and development from breakthrough discoveries in science such as hES cells will continue to be encouraged.

Question. Why should any one company be permitted to own the rights to something as potentially important and valuable as the hES cell?

Answer. hES cells that exist outside the body in culture are derived by a specific and novel laboratory process, and do not exist in nature, so are therefore patentable. Geron will continue to invest in product development based on this discovery. Aca-

demic researchers will also work with the cells to develop other potential therapeutic uses for them.

Ethical/Social Issues

Question. Is it possible that using ES cells will eliminate or reduce the need to rely on controversial methods of research?

Answer. hES cells are expected to provide an immediate source of material for the development of cells and tissues for application in transplantation therapies. As such, hES cells could help relieve the need to continually resource primary human fetal-derived tissues.

Question. Who should control and regulate the use of this technology?

Answer. The US Food and Drug Administration is the appropriate regulatory body to supervise the clinical testing of all therapeutic products derived from hES cell technology.

STATEMENT ON HUMAN EMBRYONIC STEM CELLS BY THE GERON ETHICS ADVISORY BOARD

Background

Human embryonic stem (hES) cells have been derived and subsequently maintained in tissue culture. The hES cells are isolated from donated preimplantation embryos (technically, from the inner cell mass within the blatocyst) produced through In Vitro Fertilization for clinical purposes. Institutional Review Boards (IRBs) have approved the research. All the cell research is conducted within the guidelines of the 1994 report of the NIH embryo research panel and the 1997 National Bioethics Advisory Committee report.

What makes the hES cells unique and important is that they are:

1. Pluripotent
2. Self-renewing
3. Expressive of the enzyme telomerase
4. Normal in chromosomal structure

Because of these features, these hES cells have the potential to make distinctive contributions to:

1. Understanding developmental biology (e.g., how tissues differentiate)
2. Pharmaceutical research (e.g., drug discovery and testing)
3. Transplantation medicine (e.g., generation of heart muscle cells, bone marrow, etc.)

There is no intention to use the hES cell lines for cloning a human person, transfer to a uterus (they could not develop into a fetus), or generating human-human or human-animal chimeras (mixing cells of different individuals or species).

STATEMENT OF THE GERON ETHICS ADVISORY BOARD:

An Ethics Advisory Board, whose members represent a variety of philosophical and theological traditions with a breadth of experience in health care ethics, was created by Geron Corporation in July 1998. The Board functions as in independent entity, consulting and giving advice to the Corporation on ethical aspects of its work. The process of the Board's deliberations has included sessions informing the Board of the scientific, technical, and product development work of the Corporation. Members of the Board have no financial interest in Geron Corporation.

The Geron Ethics Advisory Board is unanimous in its judgment that research on hES cells can be conducted ethically. In order for such research to be conducted ethically in the current context, some conditions must pertain. In addition, further public discourse will be needed on a range of ethically complex questions generated by this research.

1. The blastocyst must be treated with the respect appropriate to early human embryonic tissue. Members of the Board are unanimous in taking a developmental view of the moral status of the developing human being. However, we also hold that, as human tissue, the blastocyst is to be treated with moral seriousness. Research use of the blastocyst requires justification; that justification is found in research that aims ultimately to save or heal human life. This means that such tissue is to be used only when there is an overriding good to be derived from the research. In the view of the Board, the three purposes of research (understanding developmental biology, pharmaceutical research, and transplantation medicine) qualify as such goods.

2. Women/couples donating blastocysts produced in the process of In Vitro fertilization must give full and informed consent for the use of the blastocysts in research and in the development of cell lines from that tissue. The consent process must be undertaken with care, in recognition that donors undergoing In Vitro Fer-

tilization are often vulnerable. Donors should understand the potential market implications of the research, and should be advised as to whether or not there are any proprietary rights in the tissue.

3. The research will not involve any cloning for purposes of human reproduction, any transfer to a uterus, or any creation of chimeras.

4. Acquisition and development of the feeder layer necessary for the growth of hES cell lines in vitro must not violate accepted norms for human or animal research.

5. All such research must be done in a context of concern for global justice. One of the reasons the Ethics Advisory Board supports this research is its potential to contribute to widespread accessible medical interventions to alleviate human suffering. Accordingly, in the development of this research and its applications, attention must be paid to how technologies can be developed and utilized fairly for all people.

6. All such research should be approved by an independent Ethics Advisory Board in addition to an Institutional Review Board.

This analysis applies only to the isolation of hES cells from in vitro fertilized blastocysts. The Ethics Advisory Board has not yet considered the implication of emerging research on other stem cells isolated from fetal tissues.

STATEMENT OF ERIC MESLIN, Ph.D., EXECUTIVE DIRECTOR, NATIONAL BIOETHICS ADVISORY COMMISSION

Senator SPECTER. Our final witness on this panel is Dr. Eric Meslin, executive director of the National Bioethics Advisory Commission, Ph.D. in philosophy from the Kennedy Institute of Ethics at Georgetown 1989, authored and coauthored some 40 book chapters and articles on bioethics, and is a senior research fellow at Georgetown University.

We appreciate your joining us, Dr. Meslin, and look forward to your testimony.

Dr. MESLIN. Thank you very much and good morning, Mr. Chairman. I am pleased to appear before you and offer some brief remarks on the subject of human stem cell research. Since I only learned late yesterday afternoon that I would be testifying, with your permission I will submit my written testimony for inclusion in the written record soon after this hearing is complete.

Senator SPECTER. Yes; that would be fine. We appreciate your coming. We had called upon the chairman of the commission and we did give late notice. When we reviewed our witness list, we thought that we ought to hear from you since the President had written to you and you had responded. So we thank you for coming on short notice.

Dr. MESLIN. My pleasure.

Mr. Chairman, as you know, on Thursday, November 14, President Clinton wrote to Dr. Harold Shapiro, chair of NBAC, expressing concern about the report of an apparent experiment that involved the fusion of a human cell with a cow egg. The President requested that NBAC "consider the implications of such research at your meeting next week and to report back to me as soon as possible." The President also requested that NBAC undertake a thorough review of the issues associated with human stem cell research, balancing all ethical and medical considerations.

NBAC met 3 days later on November 17 for a regularly scheduled meeting and, in response to the President's first request, included on its agenda a discussion of the human cell-cow egg experiments. I must say that the commission was aided in these discussions greatly by consultations via telephone with Dr. Ralph

Brinster of the University of Pennsylvania. Also in attendance at this meeting was Dr. West, from whom you have already heard.

Following the commission's discussions, Dr. Shapiro prepared a letter which he sent to President Clinton on November 20, a copy of which NBAC has made available to this subcommittee and is, I might add, available on our website at www.bioethics.gov.

Mr. Chairman, now that the commission has responded to the first of the two requests made in President Clinton's initial letter, we are now turning our attention to preparing a comprehensive report on the ethical, legal, scientific, and medical issues arising from research involving human stem cells. We intend to complete this report as quickly as possible and very likely by early spring.

The commission next meets on January 19 and 20 of the coming year and we have already decided to devote the majority of our meeting to this subject. As with all commission reports, we intend to consult widely with the public, with scientists, with health professionals, with bioethicists, with industry, Government officials, and others who can provide us with the benefit of their wisdom.

PREPARED STATEMENT

In particular, NBAC looks forward to working with you and your subcommittee in the coming months, and I would be delighted to extend my staff's offer to work with your staff and to brief them on our work as we seek their input.

Thank you very much, Mr. Chairman, for the opportunity to appear before you this morning.

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

[The statement follows:]

PREPARED STATEMENT OF ERIC M. MESLIN

Good morning Mr. Chairman and distinguished members of this subcommittee. My name is Eric Meslin. I am the Executive Director of the National Bioethics Advisory Commission, also known as NBAC. I am pleased to appear before you this morning and offer some brief remarks on the subject of human stem cell research. However, since I only learned late yesterday afternoon that I would be testifying, with your permission, I will submit my written testimony for inclusion in the written record soon after this hearing is complete.

Mr. Chairman, as you know, on Thursday, November 14, 1998, President Clinton wrote to Dr. Harold T. Shapiro, Chair of the National Bioethics Advisory Commission, expressing concern about the report of an apparent experiment that involved the fusion of a human cell with a cow egg. The President requested that NBAC "consider the implications of such research at your meeting next week, and to report back to me as soon as possible." The President also requested that NBAC "undertake a thorough review of the issues associated with * * * human stem cell research, balancing all ethical and medical considerations." A specific time frame was not given for this latter study.

NBAC met three days later, on November 17, 1998 for a regularly scheduled meeting, and in response to the Presidents first request, included on its agenda a discussion of the human cell/cow egg experiments. [The Commission was aided in these discussions by consultations via telephone with Dr. Ralph Brinster. Also in attendance at this meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions.]

Following the Commission's discussions Dr. Shapiro prepared a letter, which he sent to President Clinton on November 20, 1998, a copy of which NBAC has made available to this subcommittee.

Mr. Chairman, now that the Commission has responded to the first of the two requests made in President Clintons letter, we are now turning our attention to preparing a comprehensive report on the ethical, legal, scientific and medical issues arising from research involving human stem cells. We intend to complete this report by late spring 1999. The Commission next meets on January 19–20, 1999 and will

devote the majority of our meeting to this subject. As with all Commission reports, we intend to consult widely with the public, with scientists, health professionals, academics, industry, government officials and others who can provide us with the benefit of their wisdom. In particular, NBAC looks forward to working with you and your subcommittee in the coming months. I would be delighted to work with your staff to brief them on our work and seek their input.

Thank you very much Mr. Chairman for the opportunity to appear before you this morning.

FETUS DESTRUCTION

Senator SPECTER. Mr. Doerflinger, you stated that the fetus destruction should not be geared toward research. If fetal material is available, then, in a manner which does not arise from being geared toward research, do you find that research acceptable?

Mr. DOERFLINGER. For Federal funding?

Senator SPECTER. Yes.

Mr. DOERFLINGER. We do not, though I understand that is the current law. I have no reason to believe that Dr. Gearhart's experiment would not have qualified under that part of the law in terms of obtaining the tissue only after the abortion and not getting involved in the informed consent process of the woman and so on.

Senator SPECTER. Why do you make the distinction, as you did in your testimony, that there is a difference, as I understood your testimony, where there is fetal destruction geared toward research contrasted with fetal destruction which is not geared toward research? You think there is a significant distinction there?

Mr. DOERFLINGER. I think the law recognizes a distinction, because it requires that if the tissue research is going to be federally funded there cannot be any influence upon the timing, manner, or method of the abortion on the part of the researcher. This is designed as a way of creating a kind of wall of separation between the research on the subsequent tissue and the actual abortion.

We think that wall is rather porous. We believe that when Government requisitions tissue from abortions generally it collaborates with an industry we do not think it should be collaborating with, and it tends to legitimize abortion as a way to produce useful material. We also think that the avenues for getting these tissues from other sources, such as miscarriages and ectopic pregnancies, have not been sufficiently explored. The Bush Administration began to fund a project in exploring those avenues, but that was shut down by the Clinton Administration before it produced any results.

I think the issue, though, is also raised with regard to the use of the stem cell lines from the Wisconsin experiment, because even though it does not involve what we would ordinarily call an abortion, it does involve destroying embryos to get the stem cells. The current fetal tissue law does cover embryos as well as fetuses, but it speaks in terms of induced abortion instead of in terms of destruction in the laboratory. I think that nobody was thinking of this then when they framed the law.

But the question is whether these embryos were destroyed in a certain way, in a manner and timing that is geared toward producing these cell lines. If that is the case, then does it not violate that wall of separation that the Congress was trying to create between the motives for destroying the embryo and the motives for using the subsequent tissue?

Senator SPECTER. Well, I think you raise a very valid point when you raise the porous issue if there is a subterfuge here. You think there may be some line, as fetal tissue from miscarriages where, as you put it, it would not be a porous line, but one which could be determined that the fetal tissue was not obtained for experimental purposes, but happened in the natural course where the fetus could not survive?

Mr. DOERFLINGER. Well, that is right. If the tissue is available because of death by accident, there is no question of mixed motives or collaborating with the decision to destroy. I should mention that it is footnoted in my longer statement that the National Catholic Bioethics Center did a book-length study of this in league with Dr. Maria Macheta of Georgetown University and was able to determine that Catholic hospitals would be willing to provide the resources for obtaining tissue of that kind that is not from induced abortion and of banking it so that cell lines could be developed that might be useful in these areas.

Senator SPECTER. Mr. Doerflinger, you also made a distinction between embryos at, I think you said, implantation contrasted with pre-implantation. Was that your testimony?

Mr. DOERFLINGER. That is a distinction that is in the current regulations. The current regulations, the Code of Federal Regulations, protects the embryo from implantation onward. The effect of the appropriations riders that have been in effect for the last 3 years was to extend similar protection to the embryo in the laboratory who has not been implanted in the womb.

Senator SPECTER. Well, that raises the question which Dr. Caplan testified to, and I appreciate your view on it, where he characterized the situation as tissues to be otherwise destroyed or tissues not to become human beings. If you take his definition on an embryo, where it is not to become a human being and it is to be otherwise destroyed, do you see an ethical objection to using the embryo in that circumstance?

Mr. DOERFLINGER. Yes; I think the nature of the moral argument here—and it is something Congress debated at some length in 1995—is because someone else in the private sector ultimately plans to discard this embryo, why do we not destroy it ourselves? To be quite frank, Mr. Chairman, I think you could leave as chairman of this committee and close down the committee if that is the basis on which this committee is going to make decisions, if you are going to just fund something that anybody else in the private sector is going to do anyway.

But what we think is that when Congress appropriates funds it decides there are certain things out there that, even though other people are going to do them anyway, we are not going to do with the taxpayers money. That is why we have bans on abortion funding even though abortion is legal.

The analogy limps a bit here because in this case two of these three experiments I believe would not be legal in your home State of Pennsylvania. They would be felonies.

Senator SPECTER. Well, this committee or subcommittee is not, No. 1, about to close down; No. 2, not about to make decisions——

Mr. DOERFLINGER. I hope you do not.

Senator SPECTER. What we are going to do is ask some questions and try to figure some things out. Then, if we think we know enough, then we will consider making some decisions.

Mr. DOERFLINGER. Could I add one point on that, because it is something that came up 3 years ago quite a bit. When the effort was made in the congressional debate to protect only against the special creation of embryos for research and to allow harmful research on so-called spare embryos, we found a number of statements from people who run the IVF clinics who were willing to say that the distinction was meaningless. Basically, if you allow the research on spare embryos, then when they do the IVF work, the in vitro fertilization work, they will just make more of them up front and make sure that they will have spares left after the fact.

In Australia and the United States, people who run these clinics are saying this. So it is an ineffectual distinction to make in terms of funding policy, I think.

Senator SPECTER. Well, I can understand that, and if you are dealing with subterfuges that is something that you have to deal with. But before we get to the subterfuge, which I think we would all agree is inappropriate what I am trying to get are your views on some of the basic points.

You think that an embryo ought not to be used for research even if it is going to be destroyed under circumstances which have integrity, where you do not make more than you need or you are not having a subterfuge, but there is a genuine fertilization issue and embryos have been created and now they are not to be used, but are to be destroyed? If that is factually true, would you say that in the private sector it is unethical to use those embryos for research purposes?

Mr. DOERFLINGER. Yes; I do not think the fact that someone else plans to mistreat human life creates any moral burden on you to go ahead and mistreat that life yourself. I believe that that is the principle that Congress has enacted in various ways in the course of debates on fetal research.

Senator SPECTER. I am making a distinction now between public funding and private funding.

Mr. DOERFLINGER. I understand.

Senator SPECTER. I asked you the question as to private funding. Do you think that——

Mr. DOERFLINGER. I am just making an ethical point which would apply to either.

Senator SPECTER. Which would apply to both?

Mr. DOERFLINGER. Yes; It seems to me that one of the things that Congress did in 1985 to clarify the Federal regulations was to say, even if it is crystal clear that someone is intending to have an abortion, the fetus that is going to be subject to that abortion should not be treated by the Government as deserving any less protection from research harm, research risk, than an embryo or fetus intended to be carried to term.

So this was a statement of moral principle. People make individual decisions out in the private sector. There are times when you cannot do anything about that. But even when that child has been abandoned by his or her own parents, that does not give the Government a moral warrant to go and do harm by itself.

Senator SPECTER. Thank you very much.

Senator Harkin.

Senator HARKIN. Thank you very much, Mr. Chairman.

I want to ask the scientists who are here. Again, I want to focus back on the issue that I brought up with the other panel initially, and that is whether or not under the reading of the ban on embryo or embryo research—you were here, you heard me read it. I will read it again. Section 511: "None of the funds made available in this act may be used for the creation of a human embryo or embryos for research purposes; research in which a human embryo or embryos are destroyed, discarded, or knowingly subject to risk of injury or death greater than that allowed for research on fetuses in utero under" other sections of the law. "For purposes of this section, the term human embryo or embryos includes any organism, not protected as a human subject under 45 CFR 46."

I asked all of the scientists who were here before the question of whether or not these stem cells are organisms. And I believe the record will show they all said no, it is not an organism.

Would that be your view, Dr. Meslin?

Dr. MESLIN. I cannot speak on behalf of the commission since we did not deliberate about the ban during the several hours that we devoted to our discussion——

Senator HARKIN. You did not go to the law and look at that?

Dr. MESLIN. Not in the 2 hours that we spent deliberating in response to the President's request. We considered it as an issue that we felt was important to raise in the context of our longer study and we intend to look at that very carefully in the coming months.

Senator HARKIN. Dr. Okarma.

Dr. OKARMA. My view is that these cells are clearly not organisms. They are highly derived by a laboratory process that took years to develop, and, in fact, as we have said, are not the cellular equivalent of an embryo. Were these cells to be implanted, they would not form a conceptus nor develop.

Senator HARKIN. Dr. Caplan.

Dr. CAPLAN. Absolutely not an organism. Stem cells lack the capacity to become viable, independent, interrelated, functioning entities, so they are not organisms.

Senator HARKIN. Let me ask the nonscientist. Mr. Doerflinger?

Mr. DOERFLINGER. Thank you. Stem cells are not organisms. However, two of the three experiments that were discussed here were not experiments on stem cells. They were experiments to get stem cells, by in one case creating and then destroying embryos, organisms, and in the other case taking embryos already in existence and destroying them.

In the Gearhart experiment, the question is whether what he has created in that tissue culture is only stem cells or in some cases is organized enough to be an embryo. He says in his study that these bodies in the tissue were forming "complex structures closely resembling an embryo during early development," and that "they appear to recapitulate the normal developmental processes of early embryonic stages."

So I think that it is an open question with regard to Dr. Gearhart's experiment whether in the course of this experiment he is actually creating some early embryos in the culture. I think the

answer is no, but I do not know and I do not know that anyone knows.

The other experiments clearly involve the laboratory manipulation and destruction of human embryos, which are protected organisms.

Senator HARKIN. What was that last thing you said? The other ones are not?

Mr. DOERFLINGER. The other two experiments, the Massachusetts and Wisconsin experiments, clearly involve the destruction of human embryos, which are organisms, in order to obtain from them stem cells, which are not organisms.

Senator HARKIN. I did not think that was true of the Massachusetts.

Dr. CAPLAN. I do not think it is true, either, in the sense in which——

Senator HARKIN. It was not true. Mr. Doerflinger, you may be closer on the other one, but certainly not Massachusetts.

Mr. DOERFLINGER. Massachusetts, because it is a cow cell?

Senator HARKIN. No, no, no.

Mr. DOERFLINGER. I could cite you——

Senator HARKIN. Dr. West, where did you get your cell from, your stem cell? Was it from an embryo?

Dr. WEST. Well, it was from an aggregation. It was the product of somatic cell nuclear transfer, creating a small group of cells. Its status as an embryo would be a matter of debate. I think it is impossible to answer at this point.

Mr. DOERFLINGER. I think it has been answered. We have a fact sheet which I would be happy to append to my testimony, in which most of the leading scientists involved in somatic cell nuclear transfer say that when you put a somatic cell nucleus, properly prepared, into an enucleated egg what you produce is an embryo. It is only because it produces an embryo that we are here debating human cloning at all.

Dr. CAPLAN. Just as a quick comment about what is in the dish, which is what we are talking about now, it would be optimistic for anybody to say that what was created in the Massachusetts report, No. 1, is not published; No. 2, is not verified. But more to the point, we do not know actually what the capacity or what will happen if that particular creation or construct, if someone attempted to grow it out.

When I was testifying before, I suggested that humility rather than bright lines might be what we want to bring to this discussion. It is possible that someone in Massachusetts could culture out something from what was in that dish. We have no idea.

Senator HARKIN. It seems to me, then, that looking back on where we have been on fetal tissue research, which was banned for a number of years and then it was lifted. We had the ban and then it became I think clear to a lot of us in the Congress and in the administration and in the scientific community—I heard for years about the problems that this ban was causing.

So we lifted the ban, but we replaced it with very strong Federal guidelines. So maybe that is what we are looking at here—not a ban but putting down strict guidelines as to what can be done with this.

Dr. CAPLAN. If you were headed in my direction, I would say it does seem to me that the two key moral categories of what we are talking about this morning are what are the sources of stem cells and where do they come from. There are issues there about the use of embryos. I tried to suggest in my oral and written testimony that it is wrong to say that all embryos are alike.

I will repeat what Senator Specter drew out of my testimony: It does not seem to me ethically sound to treat embryos destined for destruction, that no one wants to use, or embryos derived from tissues that have already been destroyed, from fetal gametes, as on a par with specially created human embryos at the IVF clinic that you intend to make a baby from. I do not believe the same moral framework ought to be applied there.

It does seem to me that if we want to understand how best to responsibly use stem cell research technology, the more public, the more accountable, the more oversight we have got, that is the way we are going to be able to make the judgments. If we let it just stay private, not only will it be slow, it will be hidden, it will be secret, and we will not know what people are doing with these materials. I think that is not the desirable outcome from a public policy point of view.

Mr. DOERFLINGER. I do not know, if I can respond to that question as well. I think guidelines may be appropriate in cases where you are dealing with tissue that is already tissue, it is already from someone who is already dead. What they are talking about is setting guidelines for how and when to make and destroy human embryos, and I do not think guidelines alone are sufficient for that.

I just want to note that in Dr. West's testimony he said that the purpose of his experiment is to allow for "the production of a blastocyst-staged embryo genetically identical to the patient who donated the nucleus, which then is harvested for its stem cells." If you ask are the stem cells an organism, the answer is no. If you take my heart out, it is not an organism, either. But the question is the experiment involves ripping out the cells from what was before a living organism.

Senator HARKIN. Well, we can go into this for a long time. The fact is is that we have thousands of embryos now all over the United States that are frozen in nitrogen and they are obviously going to be destroyed. Let us face it, OK. You are not going to keep them forever and ever and ever.

So if there is a potential of getting the stem cells from those and using those for the research, what is wrong with that? Why should we not?

Dr. CAPLAN. It is not actually thousands; it is tens of thousands.

Senator HARKIN. I do not know how many.

Dr. CAPLAN. They seem to be wards of the utility company at this point, as long as the electricity holds out.

Senator HARKIN. If these stem cells are indeed—I do not know what the proper word—self-replicating, they can keep growing——

Dr. CAPLAN. Immortal, immortal.

Senator HARKIN. Immortal. Then it would seem to me that we already have, Mr. Doerflinger, a source that is already going to be destroyed, that were not produced for this purpose because this purpose did not exist before.

Dr. CAPLAN. Senator, just to add two points about that. One, these are embryos that were not created with any eye toward exploitation of research.

Senator HARKIN. Exactly, exactly.

Dr. CAPLAN. And I have talked before coming here today with as many in vitro fertilization clinic personnel as I could, and they say that after a prolonged period of time, say 4 or 5 years, they are not going to use these embryos. They do believe there is a diminishment in their ability to become anything. So not only are we talking about embryos that are fated not to be put into any human being, we are talking embryos that specialists would not use in any human being.

So it does seem to me again morally a different status applies here. I know we have debated this in the past and will undoubtedly revisit it again, but I want to say it does seem to me that that source for stem cells is very different from a specially created circumstance where we head out to make them to use them.

Senator HARKIN. This may be a topic for another hearing, Mr. Chairman, and I know you want to wrap this up.

There is one other area, I am just going to make a statement on it, but I believe it is going to really compel us, Mr. Chairman, to have some further hearings on this. It has not to do with ethical and moral implications of what we are doing here. It has to do with the legal implications, of patent laws.

The article in the Post this morning pointed out that, even if Congress resolves the ethical issues, there is a dispute over patents. I notice that in your testimony, Dr. Okarma, you talked about Geron's intellectual property position, saying that:" Geron's intellectual property estate in the embryonic stem cell field consists of"—dah-dah-dah— "a worldwide license to the stem cell patent estate of Dr. John Gearhart and the Johns Hopkins University. This license includes all applications of human embryonic stem cells, including diagnostic and therapeutic products."

Whew, man. I take a little issue with that one. You may not think so, and again this may take us a whole other hour and we do not have the time.

Senator SPECTER. Senator Harkin, you may be about to start a subsequent hearing.

Senator HARKIN. Well, I think, Mr. Chairman, we are going to have to have a hearing on this.

Senator SPECTER. Well, I think there are many questions which we cannot answer in the parameter of a 2-hour hearing, and we had targeted conclusion for 11:30 a.m., which is just 2 minutes away.

Senator HARKIN. I just wanted to throw it out there.

Dr. OKARMA. May I have the courtesy of a response?

Senator HARKIN. Pardon?

Dr. OKARMA. May I have the courtesy of a response?

Senator HARKIN. Sure.

Dr. OKARMA. First of all, as you may know, the bulk of patent applications, for example, in new gene sequences come not from the industry, but from academia, academic centers. Like that, the applications that we have taken license to were originated by Johns Hopkins and University of Wisconsin.

In terms of the exclusivity and the applications issue that you raised, this is a starting point. We recognize that Geron by itself could never commercialize all of the opportunities we have heard elegantly testified to today. So it is our commercial intent to create partnerships with other companies to further the development of these life-saving applications.

Furthermore, if I may use what we have done with our telomerase discovery in January of this year, where we published in Science the ability to immortalize cells, since that publication we have received and responded to over 250 requests from laboratories around the world to receive that gene, which we have sent to them and allowed, under appropriate constraining guidelines, the kind of work that could be funded, is funded by the NIH in cellular immortalization. And we would propose to perform the same kind of academic collaboration with these cells were they fundable by the NIH.

Senator SPECTER. Thank you very much for that answer, Dr. Okarma.

Senator HARKIN. We need another hearing.

Senator SPECTER. Senator Harkin suggests another hearing and I think there is a need for further hearings on this issue and others. We are on a very, very deep and complex subject and in the course of the 2 hours we cannot cover it totally.

I just want to cover one more point with you, Dr. Okarma, and that is your view on the importance of having NIH be free to engage in this kind of research. Is the private sector, illustrated by your company, sufficient to undertake this research, or do you think it is desirable to have NIH involved as well?

Dr. OKARMA. It is imperative, essential, that the NIH be involved in the development of these applications.

Senator HARKIN. We have Mr. Doerflinger's view on that. Dr. Caplan, what is your view on the issue of having NIH involved?

Dr. CAPLAN. If the NIH is not involved, the research will go more slowly, the research will be driven solely by commercial practicality, the patent policies will be locked down on basic science, which should not happen, and there will be very little accountability. The substitute virtue will be secrecy. I think it would not be sound public policy.

Senator SPECTER. Dr. Meslin, do you care to offer an opinion on that subject?

Dr. MESLIN. My own view is that it is absolutely essential that NIH play a leading role. They have been thinking about ethical issues as well as the scientific issues for many years, and we are anxious to get their views as we deliberate on our own report.

Senator SPECTER. Mr. Doerflinger, I think you have expressed yourself on this, but I want to give you an opportunity to comment further, and perhaps with some focus on the question which I do not think you have addressed, raised by others, about the desirability of having regulations and oversight, which you do not have with the private companies, although we could legislate that as well. Would you care to supplement your views on the question of NIH involvement?

Mr. DOERFLINGER. I think funding and regulation are often very appropriate to distinguish acceptable research from possible

abuses. My problem with some of the experiments discussed here is that I believe they are themselves the abuses, so I do not see any point in funding them in order to regulate how they are done.

I think the argument about it being done in secrecy would a fortiori apply to the fact that in eight or nine States, as I mentioned earlier including Pennsylvania, they are illegal already anyway. So I suppose there would be an argument for also dropping all of those criminal statutes against experimenting on embryos, but I do not think that is going to be convincing to those who think that these statutes are really protecting human life.

PREPARED STATEMENT OF DANIEL PERRY, ON BEHALF OF THE ALLIANCE FOR AGING RESEARCH

We have received a statement from Daniel Perry, on behalf of the Alliance for Aging Research, it will be inserted into the record at this point.

[The statement follows:]

PREPARED STATEMENT OF DANIEL PERRY

Chairman Specter, Senator Harkin and Members of the Committee: Thank you for the opportunity to address the matter of embryonic stem cell research. As the head of a not-for-profit group eager to find cures and preventions for the diseases of aging and overall better health and vitality for the elderly, my views on research are dictated by the medical needs of the growing population of older Americans. The Alliance for Aging Research, which I represent, works to stimulate academic, governmental and privately sponsored research into the chronic diseases of human aging. I am here to express the Alliance's view that any legislation which stops or restricts stem cell research could seriously impede highly promising research which will greatly benefit older Americans, their families and the nation as a whole.

The United States and much of the world is experiencing a profound and wholly unprecedented demographic shift toward greater longevity for human beings. Every day in our nation another 6,000 people celebrate a 65th birthday and America's Baby Boomers are entering their 50s in even greater numbers.

In the decade between ages 50 to 60, the risks to the average person of being diagnosed with hypertension, arthritis or diabetes more than triple. Over the next 30 years, the United States population over age 65 will double to at least 70 million people. Their risks to disease including cancer, stroke, macular degeneration, Parkinson's and Alzheimer's diseases are doubling every five years. The cost of these disorders—just in purely economic terms—is staggering. If you add up the costs of eight of the major diseases of aging—osteoporosis, stroke, depression, arthritis, Alzheimer's, diabetes, cancer and heart disease—the total is $573 billion annually. Only new discoveries from biomedical research hold the hope of delaying or preventing altogether these debilitating conditions, potentially saving the nation billions of dollars.

Unless scientists discover better ways to treat, postpone and possibly prevent such disabling conditions, the burden on Medicare and private insurance will be crushing as the Baby Boom generation moves into the high-risk years. Without research breakthroughs and their applications, we will be left with the equivalent of very expensive hand holding for sick older people. In truth, today's drugs and other remedies for age-related diseases are not good enough. Even the better versions of current pharmaceuticals are designed to treat only the symptoms of heart failure, arthritis, and cancer, not the root causes.

The good news is that there are signs of an historic shift in drug development. Advances in genetics research are taking us towards personalized medicines that exactly match each person's unique needs and biochemical profile. Personalized medications would be far more effective in promoting health, and far less likely to carry side effects and complications that too often make matters worse, not better, for older people.

Part of the revolution in drug discovery is that some of the largest pharmaceutical companies are ready to invest billions to produce drugs that work by postponing the onset of diseases, or prevent them entirely by shutting off their genetics switches. This has enormous potential for the geriatric population. Even a brief delay in the onset of age-related disability can translate into dramatic savings for the economy

and for the nation. For example, we estimate that postponing physical dependency among older American by just one month would save the U.S. at least $5 billion a year in health care and nursing home costs. Postponing the average onset of Alzheimer's disease by just five years would eventually save $50 billion a year in health care costs by eliminating half of all cases of that disease.

With emerging research, there is now good reason to hope that scientific understanding may some day permit new approaches to disabilities driven by the aging process itself. As the committee knows, earlier this month at the University of Wisconsin, researchers reported they had successfully derived human embryonic stem cells with the potential to be transplanted into any part of the body for therapeutic use. The Wisconsin researchers believe these cells have the potential to supply unlimited quantities of normal cells of virtually any tissue type. The unique qualities of human embryonic stem cells will give researchers powerful new tools to understand mechanisms of cell division and cell repair.

The long range benefit of this kind of research is not the unlikely possibility of greatly extended lifetimes, but the plausible use of this technology to restore damaged tissues, using self-renewing, plenipotent human cells to treat blindness, coronary artery damage, diabetes, and other diseases. The ability to maintain long-lived colonies of human cells could lead directly to cell transplantation techniques in a few years to treat Parkinson's, breast cancer, heart disease, and possibly even Alzheimer's disease. Scientists involved in this research say that embryonic stem cell technology has the potential to be used to generate an unlimited supply of healthy cells and tissues for repair or replacement in a vast range of medical uses. To deny our aging population the opportunity to benefit from this research would be a tragic reversal of dramatic recent biomedical progress toward permanent cure of diseases that compromise quality of life and which account for so much of our nation's health care expenditures.

At the Alliance for Aging Research, we view recent advances in human stem cell research as a major step toward development of "gero-technology." Gero-tech is medical science harnessing the mechanics of the aging process itself in order to develop novel processes and therapies. Ultimately these research techniques could help cure, postpone or prevent age-related diseases. The more we learn about the mechanisms of aging and the more scientific interest that goes to aging, more new discoveries will be made that could improve the health and functional independence of older Americans. It would be unwise to put barriers in the way of such research.

The Alliance supports responsible and sound biomedical research, including emerging cellular technologies, that could lead to the development of therapies for scores of age-related diseases and disabilities. At this very moment millions of older Americans are suffering from Alzheimer's, Parkinson's, cancer, diabetes and other chronic health problems of aging. Not only are they suffering, but their families and care givers are suffering too, and hoping that scientists will find cures for these devastating disease and other conditions while there is still time.

Our chances of finding new ways to prevent and cure debilitating diseases will stifled unless bio-medical research into aging matters, including stem cell research, is allowed to proceed without hindrance. Certainly, policymakers, ethicists, scientists and patient groups must discuss and debate, but in the end, it is important that we arrive at public policies that allows stem cell and other promising biomedical research to go forward.

Mr. Chairman, it is likely we will continue to be confronted with scientific advances that pose difficult social and ethical questions. The vast majority of Americans strongly support the advancement of biomedical research through the application of their tax dollars. Indeed, surveys consistently show the American people want to see even greater efforts against serious and life-threatening diseases. The present momentum in the life sciences, and the profound implications of what we are learning, will inevitably raise public concerns.

It is entirely appropriate that as the legislative body which appropriates much of the funds for medical research, and as the forum for debate over public issues, the Congress exercise its right and responsibility to set public policies concerning medical research. Surely, Congress is at its best when its actions are informed and enriched by slow and careful debate, by advice from expert sources, and when taken in respect for minority opinion.

In the case of proposals to limit any of the tools for scientific and medical research, the need for prudence is powerful, due to the complexity of the issues and the consequences for public health and well-being. Ultimately, however, I believe that it is far better for the Congress and the rest of the federal government to maintain an constructive role in the ongoing research, rather than taking any action which seeks to block it. Only in this way, can the Congress ensure that the views of the American people are heeded in the research process.

On this point, it is worth noting that the research on stem cell development was carried out in the private sector without any federal funds and without any federal involvement or oversight. It is likely that private interest in, and support for, this research will proceed ahead. We believe the federal government should be actively supporting and advancing research that hold promise for healthier aging, including the stem cell and related technologies. That support should include the development of guidelines by the appropriate federal agencies to assure the ethical conduct of this sensitive but important research.

Mr. Chairman, on behalf of the Alliance for Aging Research, I thank the committee for its consideration of this vital issue and for the opportunity to present the Alliance's views on it.

SUBCOMMITTEE RECESS

Senator SPECTER. Thank you all very much for being here, the subcommittee will stand in recess.

[Whereupon, at 11:32 a.m., Wednesday, December 2, the subcommittee was recessed, to reconvene subject to the call of the Chair.]

STEM CELL RESEARCH

TUESDAY, JANUARY 12, 1999

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

The subcommittee met at 9 a.m., in room SD–192, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter and Harkin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF MARIA FREIRE, Ph.D., DIRECTOR, OFFICE OF TECHNOLOGY TRANSFER

DEPARTMENT OF COMMERCE

STATEMENT OF Q. TODD DICKINSON, J.D., ACTING ASSISTANT SECRETARY OF COMMERCE, AND ACTING COMMISSIONER OF PATENTS AND TRADEMARKS

OPENING REMARKS OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning, ladies and gentlemen. The hour of 9 a.m., having arrived we will proceed with the hearing of the Appropriations Subcommittee on Labor, Health and Human Services, and Education.

Today we are going to move forward with the second hearing on the issue of stem cells, focusing on the provision of law which appears to bar the National Institute of Health from engaging in embryo research.

We held our first hearing on December 2, and today we are going to move ahead with the patent aspects of the issue and more testimony on the potential of stem cell research.

We regret the scheduling difficulties, where we have been constrained to make some adjustments because of the Senate's consideration of the impeachment issue, and today's hearing had been set for 9:30 a.m., but yesterday Senator Lott scheduled a meeting at 10 o'clock which made it desirable to move the hearing to 9 a.m., this morning, and we are going to do our best to conclude by 10 o'clock.

The focus of our hearing today will center on a number of issues. One of them is whether stem cells are defined as an end product, which may be the contention of the companies who seek patent pro-

tection, contrasted with a classification of stem cells as a research tool, which would be a designation to promote freer dissemination among researchers.

I am a little disappointed that the Geron Corp., declined to testify today, and a number of other major associations have considered it too soon to come forward at this hearing because their public policy committees have not yet taken a position on stem cell research. It is my hope that we might move legislation to lift the ban at a very early stage because of the urgency involved here with the potential for stem cell research, which deals with so many serious diseases.

I think every day that we lose on lifting the NIH ban costs lives, perhaps every hour that we lose costs lives, so I want to see if we cannot move this legislation. That is why we held the hearing in December, shortly after the research discoveries were announced, moving ahead at this early date to be ready, and the Congress moves to the legislative agenda.

I want to now call our first panel, Dr. Maria Freire, Director of the Office of Technology Transfer at NIH, and Mr. Todd Dickinson, Acting Commissioner of Patents and Trademarks, if you would step forward.

Dr. Freire is the Director of the Office of Technology Transfer for NIH, and oversees the patenting and licensing activities for NIH and the development and implementation of technology transfer policies and procedures.

She received her Ph.D., in biophysics at the University of Virginia. Full statements will be made a part of the record. We are going to observe the 5-minute rule to allow the maximum amount of time for questions and answers. Thank you for joining us, Dr. Freire, and the floor is yours.

SUMMARY STATEMENT OF MARIA FREIRE

Dr. FREIRE. Good morning, Mr. Chairman. I appreciate the opportunity of being here today, and I am here to address how intellectual property considerations affect basic science and the future development of products for public benefit.

This morning I will focus on three issues, first how technology is transferred from the not-for-profit to the private sector, second, how this applies to stem cells and stem cell technology, and third, the implications for basic research.

TECHNOLOGY TRANSFER LEGISLATION

Let me start briefly by describing two laws enacted 20 years ago that encourage universities and Government laboratories to commercialize their research. These laws are the Bayh-Dole Act and the Stevenson-Wydler Act, including one of its amendments, the Technology Transfer Act. In general, these laws allow the laboratories and the recipients of Government funding to elect title to their inventions. They also impose certain obligations, to promote utilization, to encourage commercialization, and to ensure public availability.

In the biomedical arena, the impact of these statutes has been, indeed, dramatic, and many experts believe that it is the close relationship between the academic sector and the private sector that

has spawned the biotechnology industry. Value to the public is also very important as new drugs, vaccines, diagnostics, and medical devices of course result from this close interaction.

These activities have also stimulated economic development, and they have generated jobs in the United States.

The University of Wisconsin provides a very good example of how the Bayh-Dole Act is implemented. Early work by Dr. Thomson on nonhuman primates, such as rhesus monkeys, was federally funded. In accordance with the law, the invention was disclosed by the university to the NIH, the university filed a patent application, and the technology was licensed to a small company.

Because Federal funds were used, the Government has a nonexclusive royalty-free right to use patented cells by or on behalf of the Government. This allows Government laboratories and their contractors the right to use patented cells for further research.

In contrast, when research is funded entirely by the private sector, as is the case of Dr. Gearhart's work, the Government has no license, and it is strictly a private matter whether and under what terms new intellectual property is made available to others.

RESEARCH TOOLS

Let me point out that the fact that there exists a patent is usually not what raises concerns in the biomedical community but, rather, it is the way the patent holder chooses to exercise his or her rights on the patent.

For example, the discovery may be a research tool or a new procedure, primarily useful as a means to conduct further research. Such discoveries are commonly known as research tools. These tools may be patentable and, indeed, they have economic value for the holder of the patent.

In our view, however, the value to society is greatest when research tools are made widely available to scientists. But, therein lies the quandary. What is a research tool to one is a product to another.

Those of us working in this field strive to promote the balance between commercial interests and the public interest. For example, research tools can also be therapeutic products. Licenses can be crafted by scope and field to allow research uses without destroying commercial incentives.

The NIH, indeed, has been concerned with this issue for a good while, and Dr. Varmus put in place a national work group to study the issue and make recommendations. We will set forth guidelines for public comment in February in the Federal Register.

So how does this relate to the pluripotent stem cells? Stem cells are research tools today, and hopefully they will also be developed into therapeutic products in the future. We understand that both Johns Hopkins and Wisconsin licenses to Geron are exclusive at this time, but may allow for use of these cells by nonprofit researchers under certain terms and conditions.

There is no direct role of the NIH in these negotiations and these agreements. However, it is our view that these licenses can be crafted to ensure commercial and research purposes be both preserved.

PREPARED STATEMENT

For example, licenses can be crafted nonexclusively and they should be negotiated whenever possible to allow and assure that the research tools are available for researchers as well as preserve the commercial applications. It is important to reiterate, however, that when only private funding is involved the NIH has very little ability to obligate the universities to abide by these guidelines.

Mr. Chairman, I would be pleased to answer any questions.

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

[The statement follows:]

PREPARED STATEMENT OF MARIA C. FREIRE, PH.D.

Mr. Chairman and members of the subcommittee, I am Maria Freire, Director of the Office of Technology Transfer at the National Institutes of Health (NIH). I am pleased to appear before you today to address how intellectual property considerations affect basic science and the future development of products for public benefit.

I understand that the subcommittee is particularly interested in how patent rights and commercialization strategies operate in the context of the recent findings on pluripotent stem cells reported by Drs. John Gearhart from Johns Hopkins University and James Thomson from the University of Wisconsin. You have previously heard from a panel of experts, including the Director of NIH, Dr. Harold Varmus, on the scientific implications of these findings. Given the complexity of these issues, it is important to understand how the transfer of federally funded technology from the not-for-profit sector—be it university or Federal laboratory—to the private sector, is accomplished. To do so, I direct you to the successful process established by Congress in the 1980's that governs the commercialization of federally funded biomedical research.

The Bayh-Dole Act, Stevenson-Wydler Technology Innovation Act of 1980, and amendments, including the Federal Technology Transfer Act of 1986 (FTTA)

Nearly twenty years ago, Congress enacted a series of laws that encourage government owned and government funded research laboratories to pursue the commercialization of the results of their research. These laws are the Bayh-Dole Act of 1980, the Stevenson-Wydler Innovation Act of 1980, including one of its amendments, the Federal Technology Transfer Act of 1986 (FTTA). The Bayh-Dole Act addresses intellectual property rights in federally funded grants, contracts and cooperative agreements, while Stevenson-Wydler and the FTTA address intellectual property of government laboratories. The goal of these laws is to promote economic development, enhance U.S. competitiveness and benefit the public by encouraging the commercialization of technologies that might otherwise not be developed into products due to the lack of incentives. Generally, these laws allow government laboratories and the recipients of government funding to elect to retain title to their inventions. They also impose certain obligations: promoting utilization, encouraging commercialization and ensuring public availability of these technologies.

I am pleased to say that these goals have been achieved and expectations have been surpassed. Indeed, in the biomedical arena, the impact of these statutes has been dramatic. Many experts believe that the biotechnology industry was spawned from the close interaction between academia and industry. The Bayh-Dole Act and the FTTA continue to contribute to the global leadership of the U.S. biomedical enterprise. New products developed under this system benefit patients daily and provide hundreds of scientists with the tools required for further discovery in support of our public health mission. The NIH intramural program alone has over 150 products on the market, including diagnostic kits, vaccines, therapeutic drugs and dozens of antibodies, cell lines and other research tools. Statistics on the remarkable success of university-based technology transfer activities are also available and I have submitted a recent survey for the record.

To accomplish the transfer of technology, universities have relied on authorities granted to them by the Bayh-Dole Act. The Act permits the grantee to retain title to intellectual property developed with federal funds and to license its rights to for-profit entities. Patents provide the right to exclude others from making, using, or selling a new invention for the life of the patent. This is society's reward to the owner for teaching others how to make and use the invention claimed in the patent. In the biomedical field, patents are extremely valuable to companies, particularly small companies. They provide a means of securing investment income by estab-

lishing the company's preeminence in a particular area of technology. Parties interested in practicing an invention, in which they have no ownership, may obtain rights to the invention by entering into a licensing agreement with the patent owner. A license is a contract with binding commitments on each party, usually involving compensation. A license does not grant title to the invention. Licenses can be exclusive, when only one party is permitted to benefit from the use of the technology, or non-exclusive, when more than one party is allowed to benefit from such rights.

As this subcommittee well knows, new drugs and vaccines are costly to develop; companies will not invest in further research and development without some promise of future product exclusivity. When Congress gave federal grantees the ability to patent and exclusively license government-funded inventions, the private sector turned its attention toward publicly supported research as a new source of potential products. The value to the public resides in the generation of new drugs, vaccines, and medical devices. These activities have also stimulated economic development and the creation of new jobs in the United States.

The University of Wisconsin provides us with a good example of how the Bayh-Dole Act is implemented. Early work by Dr. Thomson on non-human primates, such as Rhesus monkeys, was federally funded and therefore, the patent obtained on stem cells arising from this work is governed by this Act. In accordance with the law, the invention was disclosed to the NIH, a patent application was filed by the University, through the Wisconsin Alumni Research Foundation (WARF), and WARF licensed the technology to a small company (Geron). Because federal funds were used for this non-human primate work, the government has a non-exclusive, royalty-free right to use the patented cells by or on behalf of the government. This would allow the government laboratories and contractors the right to use the patented cells for further research. In addition, in handling this invention the University must ensure that the goals of the Bayh-Dole Act—utilization, commercialization, and public availability—are implemented.

When research is funded entirely by the private sector, the government has no license, and it is strictly a private matter whether, and under what terms, new intellectual property is made available to others for commercial or research purposes. This is the case for the Geron sponsored work conducted by Dr. Gearhart on human pluripotent stem cells derived from fetuses.

It is usually not the existence of a patent that raises concern for the biomedical research community. The concern arises when the patent holder chooses to exercise its rights through licensing in a manner inconsistent with the advancement of basic research. For example, many new inventions are not final products. The discovery may be a research material or a new method or procedure, primarily useful as the means to conduct further research. Such discoveries are commonly known as research tools. There is little doubt that these research tools may be patentable and that they are of economic value to the holder of these rights. There is also little doubt that the value to society is greatest when such research tools are widely available to scientists.

Mr. Chairman, I cannot emphasize this point strongly enough. Preserving research uses is extremely important to the advancement of science. A license that provides complete exclusivity to a technology that is also a research tool may result in some product development in the short-term, but it will close off opportunities to advance science and develop other products in the long-term. The only way to maximize the benefit to the public is to ensure that both research use and the potential for commercial development are preserved.

The professionals working in the specialized field of biomedical licensing strive to promote a balance between commercial interests and the public interest. In those instances where a research tool can also become a therapeutic product, licenses can be, and are, carefully crafted by scope, application and field to allow use by the research community without destroying a company's commercial incentive to develop the product. Careful licensing that preserves this balance, however, has not always been the case. The NIH has been concerned for some time about the potential adverse effects of restrictive licensing practices on access to research tools. Dr. Varmus convened a national workgroup to study the issue and make recommendations to the NIH. The report of the workgroup is on the NIH web site (www.nih.gov./news/researchtools/index.htm), and NIH expects to publish guidelines for NIH supported investigators this spring, in accordance with the report.

Stem Cell Research

How does this relate to pluripotent stem cells? Pluripotent stem cells provide the research community a springboard to launch numerous inquiries into the most fundamental processes of cellular growth and differentiation that underlie human de-

velopment. Elucidating these mechanisms provides the foundation for the next generation of biomedical discovery. Such discoveries will be directed toward treatment of human developmental abnormalities, regulation of uncontrolled cellular growth associated with cancer, a source of differentiated cells and tissues for transplantation therapy, and a means to identify new drug targets and test potential therapeutics, among others. Realizing the fullest potential from this new stem cell technology for the American people deserves and requires further inquiry.

Stem cells are a research tool today; hopefully, they will also be developed into therapeutic products in the future. The issuance of patents on these new discoveries by the Patent and Trademark Office may not necessarily have an adverse effect on continuing research, provided that the patent owners devise a licensing strategy that will allow basic research to continue unencumbered while preserving commercial value. We understand that both the Johns Hopkins and Wisconsin licenses to Geron are exclusive at this time, but may allow for the use of these cells by nonprofit researchers under certain terms and conditions. These terms and conditions would be set forth in an agreement commonly called a Material Transfer Agreement, or MTA.

MTAs are vehicles used to transfer proprietary materials between and among the for-profit and not-for-profit sectors. While most MTAs are simple, 1- to 2-page agreements, MTAs can sometimes pose problems due to the type of obligations or restrictions imposed by the provider of a material on the recipient. Such obligations can stifle the broad dissemination of new discoveries, slow the technology transfer process and limit future avenues of research and product development. Examples of such obligations include so-called "reach-through" provisions that may: (1) give the provider of a material ownership of new inventions developed by the recipient; (2) require royalty payments by the recipient to the provider on inventions discovered by the recipient that are not covered by the provider's patent; or, (3) require options to exclusive rights to any new intellectual property arising from recipient's use of the material. The NIH has minimal authority with regard to the stem cell patent and patent applications at issue today, and it would be inappropriate for me to try to comment on specific terms and conditions that may be imposed by these parties under the MTAs contemplated.

At NIH, our view is that conditions imposed by patent owners—whether in a license or an MTA—can be crafted to ensure both research uses and commercial development. For example, our strategy is to negotiate non-exclusive licenses whenever possible. This allows more than one company to develop products using a particular technology, products that may ultimately compete with each other in the marketplace. We recognize that companies need an exclusive market to offset the risk, time, and expense of developing biomedical diagnostic or therapeutic products. However, companies do not necessarily need to achieve that position solely by exclusively licensing a government technology used to develop the product. Instead, companies are frequently able to add their own proprietary technologies to the invention licensed from the government to ultimately achieve some level of uniqueness and exclusivity for the final product.

If non-exclusive licensing does not provide enough incentive for the company to develop a product, and it often does not for a potential therapeutic application, NIH will award exclusivity for specific indications or fields of use, based on the license applicant's commercial development plans at the time of the application. NIH also requires exclusive licensees to grant sublicenses to broaden the development possibilities when necessary for the public health. Finally, NIH insists on the continuing unencumbered availability of the licensed technology to not-for-profit scientific community for further research.

Experience over the last 20 years has shown that to maximize public health benefit, the balance between exclusivity and access must be carefully maintained and research uses of new technologies must be preserved. These concepts form the basis for the licensing policies of the NIH, as well as for the proposed guidelines for our grantees mentioned above.

Summary

Congress has enacted legislation for recipients of federal funding that encourages the utilization, commercialization and public availability of federally funded inventions. Grantees have exercised broad discretion and appropriately seek to achieve these goals through the patenting and licensing of new inventions that arise through the use of federal funds. If the research is entirely funded by the private sector, the government has no license and is not involved in patenting or licensing decisions. Exclusive licensing, without regard to research uses, can impede rather than enhance utilization and public availability of certain types of inventions, such as research tools. Strategic licensing can alleviate potential problems. Indeed, many

grantees provide for the continuing availability of exclusively licensed subject matter to researchers in order to ensure progress of biomedical research. The NIH has urged, and will continue to urge, patent owners and exclusive licensees to ensure continuing availability under terms that do not limit basic research or encumber future products.

Mr. Chairman, I am grateful to you for providing a forum to present information about the effects of patents and licenses on this promising new area of science and medicine. I would be pleased to answer any questions you may have.

SUMMARY STATEMENT OF Q. TODD DICKINSON

Senator SPECTER. We now turn to Mr. Todd Dickinson, who is actually a doctor also, J.D., appears after his name—lawyers become doctors—Acting Assistant Secretary of Commerce, Acting Commissioner of Patents and Trademarks, B.S., degree in chemistry from Allegheny College, law degree from the University of Pittsburgh Law School, and he moved from northwestern Pennsylvania, to western Pennsylvania, to Philadelphia, to practice with the very fine law firm, Deckert, Price, & Rose, my old firm.

Mr. Dickinson, we welcome you here, and look forward to your testimony.

Mr. DICKINSON. Thank you, Senator. I want to thank you and the committee for providing the opportunity to discuss the patent system, more specifically the patenting of biotechnology that affects particularly stem cells.

It is my understanding you have been recently considering the scientific implications of this research and are now interested in investigating the patent and technology transfer implications.

The history of the U.S. patent system is a long and distinguished one. It is grounded in the Constitution. The first Patent Act was passed in the 1790's by the first Congress sitting in Philadelphia.

The premise on which the patent system is based is a simple one. In exchange for a full and complete disclosure of an invention, the Government grants a limited right in the invention to an inventor. It is not a monopoly right to own an invention as is sometimes suggested, but rather it is the right to exclude others from making, using, or selling it, and at the patent owner's discretion that right may or may not be exercised.

The public benefits from this arrangement, because full disclosure permits others to improve that technology by either developing alternative solutions or finding a better alternate species invention within the broad genus of the patent claim. This expands mankind's technological base.

Additional benefits include preventing wasteful duplication of R&D, a comprehensive teaching of the technology, and an indexing of the technology through our patent classification system.

The current patent statute dates from 1952 and specifies that to obtain a patent the applicant must meet basic statutory requirements: that the claimed invention be statutory subject matter; that it be novel, or new, that means it was not invented before; that it not be obvious to a person having ordinary skill in the art to which it pertains; and that it be fully and unambiguously disclosed in the text of the application sufficient to enable the skilled practitioner to practice it.

It is also important to remember it is a limited grant in time. The patent term runs for 20 years from the date the application

is filed. After it expires anyone is free to use it. This brings me to the specific matter of biotechnology we talked about today. Biotechnology generally and broadly encompasses any technique that uses living organisms or their components to make or modify products, to improve plants or animals, or to use microorganisms for specific usage.

As has been, I think, testified to many times, biotechnology has begun to affect our daily lives in ever-increasing ways. It is opening new pathways in the treatment of disease, and showing promising alternatives to less traditional methods.

A serious downside of research and development in biotechnology is that it is voraciously expensive, and often requires substantial time periods for commercial development. Moreover, many lines of research eventually prove to have been fruitless, yet the successful results, once known, are often not difficult to replicate by others.

Other factors, including public perception regarding things that are new and different, often keep many biotechnology inventions from reaching their full market potential. Consequently, very few biotechnology companies are profitable at this time. Many continue to require substantial additional investment to maintain their operations.

As a consequence, the biotechnology industry has a demonstrated need for patent protection to act as an effective incentive for innovation and to serve as a tangible asset for investment purposes.

One exciting development in biotechnology research has been the isolation and purification of a particular type of undifferentiated cells that can give rise to specialized functional cells. These are known as stem cells and are currently the subject of intensive research. Although most cells can only divide a limited number of times, the division of stem cells can be unlimited, so they serve as a useful tool. In addition, some are known as pluripotent stem cells and can be developed into a variety of specialized cells.

Since stem cells are both living and found in nature, a question may be legitimately raised whether they constitute patentable subject matter under section 101 of our laws. Although the question of the patentability of living organisms was answered as long ago as 1873 when Louis Pasteur got a patent on a type of yeast, 20 years ago the Supreme Court answered that question very firmly in the case of *Diamond* v. *Chakrabarty*, where they found that genetically engineered living bacteria were patentable.

They cited the congressional reports stating Congress intended statutory subject matter to include anything under the sun that is made by man. Many commentators feel this was a major factor in the growth of the biotechnology research industry.

Second, although stem cells do indeed occur in nature, they are always mixed with other cell types and do not occur in isolated or purified forms. Purified and isolated cells lines as well as methods for their purification and isolation represent important technological advances.

They may also have novel or unexpected properties or uses. A long line of case law, therefore, suggests that they may indeed result in a patent. In another regard, concerns have been raised about licensing of technology in the biotechnology area, specifically in the context of availability of research tools.

While the PTO does not normally concern itself with these issues, we have some experience in these matters and are asked to comment.

Senator SPECTER. Mr. Dickinson, will you summarize?

PREPARED STATEMENT

Mr. DICKINSON. I will do that.

Licensing can occur in a variety of ways, royalty-bearing, royalty-free, exclusive or nonexclusive. Some have speculated that licensing may adversely affect these research tools. It has been my experience that the realities of the marketplace and the goodwill of researchers very often resolve this problem very efficiently.

Senator SPECTER. Thank you very much, Mr. Dickinson.

[The statement follows:]

PREPARED STATEMENT OF Q. TODD DICKINSON

Mr. Chairman and Members of the Subcommittee: I am Q. Todd Dickinson, Acting Assistant Secretary of Commerce and Acting Commissioner of Patents and Trademarks. I want to thank you for providing me with this opportunity to discuss the patent system, more specifically the patenting of stem cells, and the licensing of technology. It is my understanding that you have recently been considering the scientific implications of research into these cells and are now interested in investigating the patent and technology transfer implications.

Background

The history of the U.S. Patent System is a long and distinguished one. Grounded in Article 1, Section 8 of the Constitution, the Patent Act of 1790 was one of the first statutes passed by the First Congress sitting in Philadelphia. The first patent was granted that same year to Samuel Hopkins, also of Philadelphia, for a method of making potash, a chemical useful for fertilizer and gunpowder—critical technologies for a new, agriculturally based nation. The application was examined by the first patent examining board: Secretary of State Thomas Jefferson, Attorney General Edmund Randolph and Secretary of War Henry Knox. The patent itself was personally signed by the President of the United States, George Washington.

The system has evolved in many ways since that auspicious beginning, and continues to serve the primary function it was intended to serve by the Founding Fathers: as an incentive to technological innovation and economic growth. From the cotton gin to the computer, America has been a model for technological development throughout its history, and patents have provided protection for the fledgling enterprises that were based on that innovation. For example, Thomas Edison still holds the record as the individual inventor holding the most patents, and his efforts led to the General Electric Co., one of the most successful and valuable corporations in the United States.

The premise on which the system is based is a simple one: in exchange for a full and complete disclosure of an invention, the government grants a limited right in that invention to the inventor or his or her assignee. It is not a monopoly right to own an invention, as is sometimes suggested, but rather the right to exclude others from making, using, or selling it. Moreover, at the patent owner's discretion, this right may or may not be exercised.

The public benefits from this arrangement since full disclosure permits others to improve that technology by developing alternative solutions, or to find a better, unexpected species invention within the broad genus of the patent claim, thereby expanding mankind's technological base. Additional benefits include preventing wasteful duplication of research and development; a comprehensive teaching of the technology, permitting it to be used efficiently after the patent term expires; and the creation of indexed databases of technology in the form of the patent classification system which permit easier and more comprehensive searching.

Studies have consistently shown that many important industries rely on a strong and effective patent system. University of Pennsylvania economist Edwin Mansfield

surveyed 100 U.S. corporations chosen randomly in six industries.[1] In each case, he asked senior management if strong intellectual property laws were a significant consideration for different kinds of investment the corporation would make in a particular country. The survey found that approximately 60 percent of companies investing in final product manufacturing facilities said that intellectual property rights had a "strong effect" on whether direct investment would be made. In chemical, pharmaceutical, or electrical equipment manufacturing, the percentages were even higher, between 74 and 87 percent. Even more telling, when executives were asked if they would invest in research and development facilities (the top end of wealth creation in an economy), 80 percent said that the strength or weakness of intellectual property rights in a country would have a strong effect on whether the company invests there.

Non-profit research institutions also benefit financially from strong intellectual property protection. The largest public university system in the United States is the University of California with over 7,000 faculty members among its 9 campuses. In 1997, the University had 2,943 active inventions. Revenues on those patent and technology licenses produced $74.7 million for the University in 1997. Carnegie Mellon University in Pittsburgh recently assigned a patent claiming spidering technology used to search the World Wide Web to Lycos for a reported $500,000 in cash, 20 percent equity in the start-up and an unspecified percentage of royalties.

In the biotechnology field, this effect is even more apparent. I recently participated in a conference hosted by members of the European Parliament who were finally successful in passing a new biotechnology patent law for Europe after more than ten years of effort. (It is reputed to be the most extended debate ever about a piece of legislation before the European Parliament.). Speaker after speaker bemoaned the fact that the absence of such legislation in Europe, and the presence of strong biotechnological patent protection in the U.S., had caused significant research and development funds, manufacturing investment, and large numbers of research scientists to relocate to the United States.

U.S. Patent Law

The current patent statute, title 35 of the United States Code, dates from 1952, and specifies that to obtain a patent the applicant must meet four basic statutory requirements: that the claimed invention be statutory subject matter (35 U.S.C. §101); that it be novel, i.e., that it was not invented before (35 U.S.C. §102); that it not be obvious to a person having ordinary skill in the art to which it pertains (35 U.S.C. §103); and that it be fully and unambiguously disclosed in the text of the patent itself, sufficient to enable the skilled practitioner to practice the claimed invention (35 U.S.C. §112). If the patent application and its claims do not meet these requirements, it is rejected. These requirements are not easy hurdles to overcome. Section 103 non-obviousness, in particular, requires a careful review of the state of the art and often very skillful crafting of claims to avoid it. In the biotechnology field, the section 112 enablement requirement is often a major stumbling block.

It should also be noted that the claims are the only legally operative portion of the patent itself. Readers of patents often incorrectly assume that the teaching of the detailed description or background of the invention found in the body of the patent in some way defines the metes and bounds of the protected invention, or that the "concept" of the invention taught in the claims is what is covered. This is incorrect. Furthermore, while the applicant may be his or her own lexicographer and define terms, undisclosed meanings not apparent in the text cannot be read into a claim and inferences cannot be drawn; the plain language of the claim alone defines the parameters of the invention. This means that claim interpretation is a difficult and often semantic art.

It is also important to remember that the patent grant is a limited right in time. The patent term runs for twenty years from the date that the application is filed. After it expires, anyone is free to use it. Furthermore, owners of patents do not necessarily have to enforce their rights: they can and do dedicate them to the public. Since a patent may not be granted on an invention known to the public for more than a year, inventors may also dedicate their inventions to the public through public disclosure without filing applications

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[1] E. Mansfield; "Intellectual Property Protection, Foreign Direct Investment and Technology Transfer"; International Finance Corporation, Discussion Paper Number 19, The World Bank, 1994.

Biotechnology and Stem Cell Research

Biotechnology generally encompasses any technique that uses living organisms or their components to make or modify products, to improve plants and animals, or to use microorganisms for specific uses. Biotechnology has begun to affect our daily lives in ever-increasing ways. It is opening new pathways in the treatment of incurable diseases and is showing promising alternatives to less effective traditional treatments. In the field of nutrition, biotechnology makes ever-greater headway to improve food production and plant breeding in a manner that one could only dream about a decade ago. In the field of genetics, the use of new techniques is beginning to open substantial and wide-ranging benefits for human and animal health, the protection of the environment and the potential for productivity gains in food, agricultural and pharmaceutical industries.

A serious downside of research and development in the biotechnology area is that it is voraciously expensive and often requires substantial time periods for commercial development. Moreover, many lines of research eventually prove to have been fruitless. Yet, the successful results, once known, are often not difficult to replicate by others. Other factors, including public perception regarding anything new and different, also keep many biotechnology inventions from reaching their full market potential. Consequently, very few biotechnology companies are profitable at this time. Many continue to require substantial additional investment to maintain operations. As a consequence, the biotechnology industry has a demonstrated need for patent protection to act as an effective incentive to innovation and to serve as a tangible asset for investment.

One exciting development in biotechnology research has been the isolation and purification of particular types of undifferentiated cells that can give rise to a succession of specialized functional cells. These are known as stem cells, and are currently the subject of intensive research. Although most non-cancerous cells can divide only a limited number of times, the division of stem cells can be unlimited and may serve as a useful tool in solving many previously intractable medical conditions. In addition some stem cells are "pluripotent" cell lines, meaning they can be made to develop into a variety of different specialized cells.

Patentability

Since stem cells are both living and found in nature, however, a question that may legitimately be raised is how they can constitute patentable subject matter under §101 of our patent law. Although the question of the subject matter patentability of living organisms may have been answered as long ago as 1873, when Louis Pasteur was granted a United States patent on yeast, it was most firmly addressed by the Supreme Court almost twenty years ago in the famous case Diamond v. Chakrabarty[2]. In that case, Chief Justice Burger, writing for the Court, found that genetically engineered bacteria useful for cleaning up oil spills by ingesting hydrocarbons were themselves patentable. As noted by the Court (citing the Congressional Report accompanying the 1952 Act[3]), "Congress intended statutory subject matter to include anything under the sun that is made by man". Many commentators believe that this case was a major factor in the phenomenal growth of the biotechnology industry. And it should also be noted that the PTO has long issued patents to living plants under the provisions of the Plant Patent Act of 1930.

Moreover, although stem cells do indeed occur in nature, most evidence indicates that they are always mixed with other cell types and do not occur in an isolated and purified form. Purified and isolated cell lines, as well as methods for their purification and isolation, represent important technological advances. They may also have novel or unexpected properties or uses, and may therefore result in a patent.[4] As stated by the Supreme Court, "To obtain a patent for a product made from raw material, it must possess a new or distinctive form, quality, or property."[5]

The patentability of biologically pure compositions has been the law for over twenty years. In In re Bergy (1977)[6], the Court of Customs and Patent Appeals (the predecessor court to the Court of Appeals for the Federal Circuit (CAFC), the appeals court to which PTO appeals are taken) ruled that a biologically pure bacterial culture was patentable, and not a "product of nature", since the culture did not exist in nature in its pure form and could only be produced in a laboratory under care-

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[2] 447 U.S. 303, 65 L.Ed.2d 144, 100 S.Ct. 2207, 206 U.S.P.Q. 193 (1980).

[3] S. Rep. No. 1979, 82nd Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82nd Cong., 2d Sess., 6 (1952).

[4] See generally Bozicevic, "Distinguishing 'Products of Nature' from Products Derived from Nature," 69 Journal of the Patent and Trademark Office Society 415 (1987).

[5] American Fruit Growers, Inc. v. Brodex Co., 283 U.S. 1, 11, 8 U.S.P.Q. 131, 133 (1931).

[6] 568 F.2d 1031, 195 U.S.P.Q. 344 (ccpa 1977).

fully controlled circumstances.[7] This has been extended since that time to "'purified and isolated' DNA sequences encoding human erythropoietin (EPO)",[8] and a preparation of Factor VIII: C, used for treating hemophilia. ("Although Factor VIII: C molecules occur in nature, a purified and concentrated preparation of Factor VIII: C as claimed in the patent constitutes a new form or combination not existing in nature, and hence is patentable under 35 U.S.C. §101.")[9]

Accordingly, it is the present position of the Patent and Trademark Office that purified and isolated stem cell lines are patentable subject matter under 35 U.S.C. §101.

Licensing

Concerns have also been raised regarding the licensing of technology in the biotechnology area, specifically in the context of the availability of research tools. While the Patent and Trademark Office does not normally concern itself with access issues, we do have responsibility for intellectual property policy generally, and, as such, have some experience in these matters.

A traditional way to exploit one's patent is to license it to others, under a wide variety of possible terms: exclusive or non-exclusive; royalty-free or royalty bearing. Patent owners may also choose not to license, for a variety of reasons, such as a desire to preserve exclusivity or maintain competitive advantage. This right is fundamental to the patent grant.

While some speculate that patent owners who refuse to license or exclusively license others may adversely affect access to biotechnological research tools, it has been my experience that market realities and/or good will almost always resolve this problem. One famous example may prove illustrative.

Almost two decades ago, Stanford University was granted a patent on a method covering basic recombinant DNA technology, the so-called Cohen-Boyer patent, U.S. Patent Number 4,237,224. Because of the fundamental nature of the technology, great public concern was raised that biotechnology research would be blocked, or that Stanford would charge such exorbitant royalty rates that research would be priced out of reach. In reality, nothing of the sort occurred. Stanford quickly developed a reasonable and widely available licensing program and alternative technologies were developed to compete with it. Because the licenses were offered at reasonable rates to all who sought them, technology was not stymied. Improvements to the technology also arose resulting in a moderating cross-licensing program.

Another question which has been raised concerns specific additional grants or limitations contained in certain licensing agreements. These include such provisions as a requirement that any improvements in the licensed technology be licensed back to the patent holder, commonly known as grant-backs. Provisions such as this are fairly common in commercial technology licenses, although they are also often the subjects of significant negotiation.

It is also important to note that many of these aspects of intellectual property licenses may be subject to antitrust scrutiny. See, for example, the Antitrust Guidelines for the Licensing of Intellectual Property, recently promulgated by the Antitrust Division of the Justice Department and the Federal Trade Commission.

In the context of these licensing considerations, it is also important to define specifically what "research tools" are being implicated in these concerns. Many of the instruments, chemicals and equipment used daily in research have patented technologies associated with them. A license to practice under those patents, and the related royalties, are often captured in the purchase price.

Last, and significantly, it should be noted that restrictions on licensing or subject matter patentability must also comply with United States international obligations. Through protracted negotiations, the U.S. has convinced many of our trading partners of the great value of intellectual property protection and has been able to reach agreement with them to provide strong intellectual property protection. In fact, we were able to incorporate our position on intellectual property protection into the Uruguay Round Trade Agreements of GATT. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) requires the United States and all other members of the World Trade Organization to provide similar patent protection for all patentable subject matter.

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[7] The Supreme Court granted certiorari, but summarily remanded to the CCPA in light of another related case. The CCPA later affirmed its earlier opinion.

[8] Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 13 USPQ2d 1737, aff'd in part, rev'd in part, vacated in part, 927 F.2d1200, 18 USPQ2d 1016 (Fed Cir. 1991), cert. denied, 112 S. Ct. 169 (1991).

[9] Scripps Clinic & Research Foundation v. Genentech Inc., 666 F.Supp. 1379, 1389 n.6, 3 USPQ2d 1481, 1487 n6. (N.D. Calif. 1897), aff'd.in part, rev'd in part, vacated in part and remanded, 927 F.2d 1565, 18 USPQ2d 1001.

We have encouraged strong pharmaceutical patent protection by our trading partners and must continue to provide strong patent protection for biotechnological inventions, such as cell lines. That protection should not be diminished by inappropriate incursions into the rights of the patent owner. In fact, U.S. patent policy toward our trading partners strongly discourages compulsory licenses or any other such limitations on a patent holder's rights.

While we certainly share concerns about access to technology, and would highly recommend that oversight of potential abuses be maintained, the balance of interests in this area is currently a carefully calibrated one, and should not be upset absent strongly reasoned analysis and demonstration of actual harm.

Summary

The United States leads the world in biotechnology research and development. We also lead the world in intellectual property protection. It is imperative to the former that we maintain the latter. As stated long ago by President Abraham Lincoln, a patent holder himself: the patent system has ''added the fuel of interest to the fire of genius.'' Our continued success as the most technologically advanced nation in the history of the world demands that we honor that system and the benefits it brings.

Thank you.

REMARKS OF SENATOR TOM HARKIN

Senator SPECTER. Let me turn, before we go to a round of questioning, to my distinguished colleague, the ranking member, Senator Harkin.

Senator HARKIN. Thank you very much, Mr. Chairman. I apologize for being a little bit late, and I thank you for convening this very important hearing. I just had a couple of statements, if I might make them here.

This really is going to help us get a much better understanding of the patenting and licensing issues, particularly as they apply to the recent discovery of human embryonic stem cells.

Last month we heard the Department of Health and Human Services General Counsel's Office was examining whether the current ban on human embryo research, whether NIH-funded scientists could conduct research on the stem cells lines isolated by Dr. Thompson and Dr. Gearhart.

As I recall, at our last hearing, every scientist present stated their belief that the stem cells are not organisms and, therefore, cannot fall under the Federal ban.

Shortly after the hearing last month, I sent a letter to Secretary Shalala requesting her timely decision on this issue, and I must say I am very disappointed that this has not yet been done and the decision has not yet been made by HHS. It seems obvious to me and every scientist who testified here last month that this research can be federally funded.

Now, with or without Federal funding, some of the research community have questioned the availability of these cells lines, questioning whether or not they can be available to nonprofit scientists. They believe the content of the licensing agreements and what some perceive to be overly broad patent claims can hinder others from using these cells lines.

Now, again, I do not pretend to know the answer to these questions. I am pleased that we have the people here today to testify on this.

I must say that I am disappointed that we did not have here today witnesses from one or more of the private companies involved in this to hear their side of the story, although I do understand, Mr. Chairman, that—at least my staff tells me that they are going

to submit a statement for the record. Can you enlighten me on that?

Senator SPECTER. Well, it is pretty hard just to have a statement for the record. It is pretty hard to have a hearing without witnesses.

Senator HARKIN. Well, I agree with you. I wish they had shown up. I would like to have questioned them.

Senator SPECTER. Or a trial without witnesses.

Senator HARKIN. Well, it depends on what kind of trial you are talking about. [Laughter.]

Are you talking about a courtroom trial?

Senator SPECTER. We can agree on a hearing with witnesses. [Laughter.]

Senator HARKIN. We can agree on a hearing with witnesses. [Laughter.]

Senator SPECTER. Senator Harkin, they have submitted a draft statement, but I commented before you arrived that I was a little disappointed that Geron did not appear.

Senator HARKIN. Well, I am, too.

Senator SPECTER. Because, without mentioning impeachment, we really need to be able to ask them questions and have a dialog, and their absence here does not help the subcommittee on moving ahead with its conclusions. We have a draft statement, and perhaps we can hear them at a later time. I think the parties are even subject to subpoena under a variety of rules in our Senate.

Senator HARKIN. Well, I am sorry, Mr. Chairman. I do not know what you want to do with that statement, whether you want to make it a part of the record. That is fine with me.

Senator SPECTER. We will make it a part of the record for whatever value it has, but I concur with you that we need them here to respond to questions.

Senator HARKIN. Well, I agree. I am glad we agree on that, Mr. Chairman, but at least we have the people who are here today and some other scientists to talk about applications of this in terms of health care. My interest in this hearing today was to get a better understanding of the Bayh-Dole Act, the Stevenson-Wydler Act, and how these apply in genetics and in the stem cell areas particularly, and what that means in terms of licensing arrangements under the patents that they hold.

I remember in 1980, when Bayh-Dole was passed, I was in the House and I was chairing the subcommittee that had jurisdiction over the National Science Foundation, and I remember at that time the problems that we had with private entities coming in, putting the money into research, and not being assured that they could have a patent or something for future recompense for the money that they had invested. That was a big stumbling block.

I remember an invention that had been developed at Iowa State University. I am searching my memory for exactly what it was, but because of the inability to obtain a patent on it, a Japanese company had come in and taken it and was manufacturing it and selling it in this country.

PREPARED STATEMENT

So that propelled us in 1980 to pass this bill to try to strike a balance between the public interest and the need to raise the private moneys to engage in this kind of expensive research so that people could be guaranteed they would get some return on that investment and to bring these products to market, to get them out of the lab and get them to market.

Our first witness said something about a dilemma. I will not go into that. I will just ask that the rest of my statement be made a part of the record.

[The statement follows:]

PREPARED STATEMENT OF SENATOR TOM HARKIN

Thank you, Chairman Specter, for convening this important hearing. I had requested this hearing in order to get a better understanding of patenting and licensing issues, particularly as they apply to the recent discovery of human embryonic stem (hES) cells.

Last month, we heard that the Department of Health and Human Services' General Counsel's office was examining whether, under the current ban on human embryo research, NIH-funded scientists could conduct research on the hES cell lines isolated by Dr. Thomson at the University of Wisconsin and Dr. Gearhart of Johns Hopkins. As I recall, at our last hearing every scientist present stated their belief that hES cells are not organisms, and therefore cannot fall under the federal ban. Shortly after the hearing last month, I sent a letter to Secretary Shalala requesting her timely decision on this issue, and I must say I am very disappointed that she has not yet been able to make a decision on this. It seems obvious to me—and to every scientist who testified here last month—that this research can be federally-funded.

But with or without federal funding, there are some in the research community who question the availability of these cell lines to non-profit scientists. They believe that the content of the licensing agreements, and what some perceive to be overly broad patent claims, could hinder others from using these cell lines. I don't pretend to know the answer to these questions, so I am very pleased that we have an opportunity to hear from patent and technology transfer experts Maria Freire from the NIH and Todd Dickinson from the Patent and Trademark Office (PTO), to get their views on the matter.

I am also glad to hear today from cell biologist Dr. Lawrence Goldstein, Mr. Richard Pikunis, who suffers from Parkinson's disease, and Dr. Douglas Melton on behalf of the Juvenile Diabetes Association. We learned a great deal from the hearing last month about the technology and methods for isolating hES cells, now is our chance to learn from the second panel about the hope this new technology offers to the millions of Americans who suffer from these diseases, and the critical need for federal funding of this research.

The ground breaking research done by Dr. Thomson and Dr. Gearhart shows tremendous promise. From enabling the development of cell and tissue transplantation, to improving and accelerating pharmaceutical research and development, to increasing our understanding of human development and cancer biology, the potential benefits of their work are truly awe-inspiring.

Therefore, my primary goal for this hearing is to make sure Congress is doing what it can to ensure that research moves forward, without unreasonable impediments or delays. However, I want to make it clear that I do not believe that research should be done solely for research's sake. We must continue to ensure that incentives are in place for promising inventions to get to market. That is why we have invested all we have in biomedical research—so that these inventions can be used to cure and treat the diseases affecting the American people. To this end, I believe the patent system and the Bayh-Dole law have been very successful.

However, as I stated earlier, some in the research community have raised concerns about their access to "research tools," which I understand include these new stem cell lines. They say that dealing with the required bureaucratic paperwork slows down their research, and that the cost of access to these tools increases the overall cost of research, which leads to higher and higher costs of the product for the eventual consumer.

Others in the research community maintain that the system works well and should not be changed. They say that without intellectual property rights, the bio-

technology industry would have little incentive to invest in the time-consuming and expensive research and development (R&D) required to bring a product to market.

I believe it would be a travesty if the potential benefits of stem cell research—or any research for that matter—are delayed or denied to patients for any reason: Whether it is because the add-on cost of access to research tools is too expensive, or because companies lack an incentive to bring a product to market. It is therefore critical that we maintain a healthy balance of incentives between the federal government, non-profit research institutions and the private sector.

I hope today's hearing will help clarify this debate.

TIME CONSTRAINTS

Senator SPECTER. In light of our time constraints, I said to Senator Harkin before you arrived that Senator Lott had scheduled the session on the impeachment issue at 10 o'clock, which is why we had moved the hearing to 9 o'clock.

Senator HARKIN. We are in session at 10 o'clock?

Senator SPECTER. No; it is not in session, it is a meeting among Republican Senators.

Senator HARKIN. An open meeting? [Laughter.]

Senator SPECTER. I think only the closing statements are open, Senator Harkin. [Laughter.]

If you missed Senator Harkin on C-SPAN last night, he was not quite as erudite as this morning, but very erudite. [Laughter.]

In the interests of time we are going to call the next panel, and if you would stay where you are, and then we will move to questions among all five of the witnesses.

NONDEPARTMENTAL WITNESSES

STATEMENT OF LAWRENCE GOLDSTEIN, Ph.D., PROFESSOR OF PHARMACOLOGY, DIVISION OF CELLULAR AND MOLECULAR MEDICINE, UNIVERSITY OF CALIFORNIA AT SAN DIEGO

SUMMARY STATEMENT

Senator SPECTER. Our first witness on the second panel is Dr. Lawrence Goldstein, professor of pharmacology at the Division of Cellular and Molecular Medicine, University of California. He serves as an investigator for Howard Hughes Medical Institute at the University of California at San Diego, Ph.D., from the University of Washington. Welcome, Dr. Goldstein, and the floor is yours for the next 5 minutes.

Dr. GOLDSTEIN. Thank you, Senator.

Mr. Chairman and members of the subcommittee, I am Lawrence Goldstein and I am here today as a representative of the American Society for Cell Biology. The society represents over 9,000 biomedical researchers throughout the United States and the world, most of whom work in our Nation's leading research universities and institutes.

As you said, my own research is conducted in the Division of Cellular and Molecular Medicine at the University of California San Diego School of Medicine.

Before moving to San Diego, I was on the faculty in the Department of Cellular and Developmental Biology at Harvard University for 10 years. My research work concerns molecular and genetic analysis of protein motors and their roles in cellular growth, function, and development.

I speak today on the need to ensure life-saving progress in medical research while simultaneously protecting ethical and moral decency. As you know, scientific advances are emerging at a blinding pace. These advances present Congress with a serious challenge. You must find a balance between on the one hand assuring the public that new knowledge will not be misused and that the ethics of such work will be carefully considered, while on the other hand ensuring that critical medical research is not impeded because of unnecessary fear or insufficient information.

The specific issue today concerns human stem cells, which have extraordinary potential to revolutionize the treatment and cure of devastating human diseases. Already, in the short time since the generation of these cells was announced, we can conceive of many important applications in the treatment of heart disease, diabetes, Parkinson's disease, and Alzheimer's disease. In fact, the list of possible therapeutic uses is almost endless.

These broad applications are likely, because it may be possible to coax stem cells to become the many types of cells often lost to the ravages of disease.

My colleague, Nobel Laureate Dr. Paul Berg of Stanford University, stated in a recent letter to you that currently only scientists who receive private, non-Federal funding may pursue stem cell research. This has the effect of excluding the majority of the Nation's most prominent researchers, who are supported by the NIH and NSF, and are based at universities and nonprofit institutions throughout the country.

The current exclusion limits the development of new therapies, and relies exclusively on the commercial sector to reap the benefits of scientific insights originally developed with the generous support of the Federal Government.

Recent work with stem cells from fetal tissue is permissible under current Federal guidelines. However, we first seek to persuade this committee and the Congress to make the informed and courageous decision to ensure that those scientists who are most prepared and best-qualified to conduct safe, ethical, and invaluable embryonic stem cell research be allowed to do so.

Allowing peer-reviewed Federal funds to be used for this type of research is our best guarantee the quality of the work will be high, and the results can be best used to serve the public good.

Senator Harkin went to great lengths at your last hearing to point out that the current ban on embryo research does not expressly prohibit federally funded scientists from conducting the research using human embryonic stem cells. We agree with the Senator's understanding, and await the Department of Health and Human Services' interpretation of the current law.

In any discussion of this issue, however, it is essential to define clearly and to distinguish among varying types of human stem cells, and there are at least two kinds.

First are totipotent stem cells, which have the theoretical and perhaps real potential to become any kind of cell and could perhaps, under appropriate conditions, such as implantation in a uterus, become an entire individual.

Second are pluripotent stem cells, such as those that can be obtained from an early stage embryo, which have a more limited potential in that they can only form certain kinds of cells such as muscle, nerve, or blood. Thus, pluripotent stem cells that are derived from the inner cell mass of a blastocyst are not capable on their own of embryological development, or the creation of a human being.

It may, though, be possible to induce these cells to form certain specialized cell types that make up important human tissues such as those of the liver, pancreas, skin, heart, and nerves, and it is this potential which makes these stem cells such an important resource to develop for therapeutic uses.

To this end, the society supports the elimination of the existing prohibition of Federal funding for research with human embryos and specialized cells derived from them. Research with human embryos obtained by ethically validated means and specialized cells derived from them should be allowed to proceed in a way that would assure the public that the cloning of a human being is prohibited, and that ethical considerations are guaranteed.

In closing, the society enthusiastically supports your efforts to highlight for the public and your colleagues in the Senate the po-

tential value of modern scientific techniques for improving human health.

PREPARED STATEMENT

Stem cell research in particular has enormous potential for the effective treatment of human disease. Thus, we believe there is a moral imperative to do it in an ethically validated manner. We must not close off scientific opportunity to those most qualified to make dramatic strides in the cure of disease through the use of stem cells.

Mr. Chairman, thank you for the opportunity to present my thoughts today.

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

[The statement follows:]

PREPARED STATEMENT OF LAWRENCE S. B. GOLDSTEIN, PH.D.

Mr. Chairman and members of the Subcommittee: I am Lawrence Goldstein. I am here today as a representative of the American Society for Cell Biology. The Society represents over 9,000 basic biomedical researchers throughout the United States and the world, most of whom work in our Nation's leading research universities and institutes.

My own research is conducted in the Division of Cellular and Molecular Medicine and the Department of Pharmacology at the University of California, San Diego School of Medicine. I am also an Investigator of the Howard Hughes Medical Institute. Before moving to San Diego I was on the faculty in the Department of Cellular and Developmental Biology at Harvard University for 10 years. My research work concerns molecular and genetic analysis of protein motors and their roles in cellular proliferation, function, and development.

I speak today on the need to ensure life-saving progress in medical research, while simultaneously protecting ethical and moral decency. As you know, scientific advances are emerging at a blinding pace. These advances present Congress with a serious challenge. You must find a balance between assuring the public that new knowledge will not be misused and that the ethics of such work will be carefully considered, while ensuring that critical medical research is not impeded because of unnecessary fear or insufficient information.

The specific issue today concerns human stem cells, which have extraordinary potential to revolutionize the treatment and cure of devastating human diseases. Already, in the short time since the generation of these cells was announced, we can conceive of many important applications in the treatment of heart disease, diabetes, Parkinson's disease, Alzheimer disease, spinal cord injury; in fact, the list of possible therapeutic uses is almost endless. These broad applications are possible because it may be possible to coax stem cells to differentiate into the many types of cells often lost to the ravages of disease.

My colleague, Nobel Laureate Dr. Paul Berg of Stanford, stated in a recent letter to you that:

Currently, only scientists who receive private (non-federal) funding may pursue [stem cell] research. This has the effect of excluding the majority of the Nation's most prominent researchers who are supported by the NIH and NSF and are based at universities and non-profit institutions throughout the country. The current exclusion limits the development of new therapies and relies exclusively on the commercial sector to reap the benefits of scientific insights developed with the generous support of the federal government.

Recent work with stem cell from fetal tissue is permissible under current federal guidelines. We further seek to persuade this Committee and the Congress to make the informed and courageous decision to ensure that those scientists who are most prepared and qualified to conduct safe, ethical and invaluable stem cell research be enabled to do so. Allowing peer-reviewed federal funds to be used for this type of research is our best guarantee that the quality of the work will be high and that the results can be best used to serve the public good.

Senator Harkin went to great lengths at your last hearing to point out that the current ban on embryo research does not expressly prohibit federally-funded scientists from conducting research using human stem cells. We agree with the Sen-

ator's understanding and await the Department of Health & Human Services' interpretation of the current law.

In any discussion of this issue, it is essential to define clearly and to distinguish among various types of human stem cells. There are at least two kinds of stem cells:

—Totipotent stem cells have the theoretical, and perhaps real, potential to become any kind of cell, and under appropriate conditions, such as implantation in a uterus, could become an entire individual.

—Pluripotent stem cells, such as those that can be obtained from an early stage embryo, have a more limited potential, including those which are more committed, in that they can form only certain kinds of cells, such as muscle, nerve or blood cells, but they cannot form a whole organism.

Pluripotent stem cells that are derived from the inner cell mass of a blastocyst are not capable on their own, however, of embryological development or the creation of a human being. It may, though, be possible to induce these cells to form certain specialized cell types that make up important human tissue, such as those of the liver, pancreas, skin, heart, and nerves. It is this potential which makes stem cells such an important resource to develop for therapeutic uses.

To this end, the Society supports the elimination of the existing prohibition on federal funding for research with human embryos and specialized cells derived from them. Research with human embryos obtained by ethically validated means, and specialized cells derived from them, should be allowed to proceed in a way that would assure the public that the cloning of a human being is prohibited, and that ethical considerations are guaranteed.

The Society enthusiastically supports your efforts to highlight for the public and your colleagues in the Senate the potential value of modern scientific techniques for improving human health. Stem cell research, in particular, has enormous potential for the effective treatment of human disease. Thus we believe that there is a moral imperative to pursue it in an ethically validated manner. We must not close off scientific opportunity to those most qualified to make dramatic strides in the cure of disease through the use of stem cells.

Mr. Chairman, thank you for the opportunity to present my thoughts today. I would be pleased to answer any questions.

STATEMENT OF DOUG MELTON, Ph.D., REPRESENTING THE JUVENILE DIABETES ASSOCIATION, HARVARD UNIVERSITY

Senator SPECTER. We now turn to Dr. Douglas Melton, chairman of the Department of Molecular and Cellular Biology at Harvard University, who also serves as an investigator for the Howard Hughes Medical Institute, and associate member of the Children's Hospital in Boston. Dr. Melton is here today on behalf of the Juvenile Diabetes Association and has an extra special interest in the issue, since his 7-year-old son was diagnosed with the disease at the age of 6 months.

Welcome, Dr. Melton. The floor is yours.

Dr. MELTON. Good morning, Chairman Specter and Senator Harkin. As you noted, I am the chairman of the Molecular Biology Department at Harvard, but I am here today both as a researcher and a father of a 7-year-old type I diabetic. I am here because I feel I can speak to you both about the human burden of diabetes and the scientific potential of stem cell research.

Mr. Chairman, before I begin my remarks on the subject of today's hearing I want to take this opportunity to thank you and other members of the subcommittee for your role, your leading role in last year's historic increase in HIH funding. The strong bipartisan support for that increase gives renewed hope to those of us who are struggling with chronic diseases on a daily basis.

Founded nearly 30 years ago by parents of children with diabetes, the JDF is a voluntary health organization that is dedicated to finding a cure for diabetes through research and, in fact, this year the foundation expects to commit nearly $65 million directly toward diabetes research.

Diabetes, as you know, is an insidious disease, and remains widely misunderstood by the public, because many people wrongly think that insulin is a cure when it is, in fact, merely life support.

Diabetes is the leading cause of new adult blindness, kidney disease, and nontraumatic amputations, and it costs this country nearly $100 billion a year. That is billion, not million; 60 million Americans suffer from diabetes and, on average, a person with the disease can expect to live 15 fewer years than those without it.

In addition, and particularly poignant to me, is that it is among the most chronic diseases affecting children, and this is a group upon which its effects are especially devastating.

Before I discuss the exciting potential of stem cell research, allow me to speak briefly to you as a parent. The daily regimen of my son Sam's blood checks and insulin injections, up to five of them a day, are coupled with our need to balance his diet and exercise. This is, as you might expect, a serious challenge in dealing with a 7-year-old soccer player.

The medical troubles for Sam are compounded by the vigilance and worry that extracts a heavy toll on the rest of my family. For example, my wife is regularly up late in the night doing blood checks while Sam sleeps and we wonder, is his blood sugar too low, will he go into a coma during the night.

I am sorry to say that I cannot recall a night of peaceful sleep since Sam was diagnosed nearly 7 years ago, and I am unwilling to accept the enormity of the medical and psychological burden, and am personally devoted to bringing it to an end for my son Sam and for all type I diabetics. I implore you to continue to make it possible to cure diabetes for diabetics and their families.

Let me now turn to the main subject of today's hearing. That is, the potential cure for diabetes as it relates to human stem cell research. As Dr. Goldstein mentioned, based on recent discoveries it is now foreseeable that human stem cells could be stimulated to develop into a number of cell types, notably pancreatic islets. These are the cells that are destroyed in a type I diabetic.

These stem cells then have the potential to develop into any tissue organ in the body, and they could no doubt be directed to make pancreatic islet or beta cells.

One of the most promising ways of curing diabetes is to restore biologically the function of the missing islet cells, and this could occur through islet transplantation, or through engineering cells such as these human stem cells.

The availability of human stem cells which could be turned into beta cells would solve two important problems, No. 1, that of insufficient islet supply, which presently plagues the field and, No. 2, the recurrence of the autoimmune response.

My written testimony details how it solves the autoimmune problem, but let me just say that by engineering stem cells it would be possible to avoid the requirement for the immunosuppressive drugs.

I would like to conclude by noting the important ethical considerations which your subcommittee has, of course, considered. The JDF and I well understand that stem cell research has important ethical considerations that need to be addressed. However, we feel that appropriate safeguards can and should be established to en-

sure that this important research can be conducted using Federal funding.

The 1994 Human Embryo Research Panel, which included both scientists and ethicists, studied the ethical issues raised by this type of research, and it is important to note that they concluded that stem cell research involving preimplantation human embryos is acceptable for Federal funding.

We believe that that panel's report provides a scientific and ethical basis to justify Federal funding for stem cell research on human material, and this report could also serve as the basis for the establishment of a set of safeguards that would ensure that this research was conducted ethically in both public and private settings while still allowing for significant advances in the fight to cure diabetes.

PREPARED STATEMENT

I will conclude, Mr. Chairman, by thanking you for the opportunity to speak today and saying that the opportunities presented by human stem cell research offer us the promise of truly significant advances and perhaps a cure for diabetes. A world without diabetes for all the children and adults who suffer from the devastating impact of this disease is the goal of the JDF, and we urge you to ensure that Federal policies allow this research to continue to speed our path to cure this disease.

Thank you.

Senator SPECTER. Thank you, Dr. Melton.

[The statement follows:]

PREPARED STATEMENT OF DOUG MELTON, PH.D.

Good morning Chairman Specter, Senator Harkin and other members of the subcommittee. My name is Doug Melton and I appear before you today on behalf of the Juvenile Diabetes Foundation International and the millions of families in this country touched by diabetes. I am Chairman of the Department of Molecular and Cellular Biology at Harvard University, but more importantly for today's discussion, I am here today because my 7-year-old son, Sam, has had Type 1 (or insulin-dependent) diabetes since he was 6 months old. I am here this morning as a father and a researcher, as someone who can speak to you about the human burden of diabetes and the scientific potential of stem cell research.

Mr. Chairman, before I begin my remarks on the topic of this morning's hearing, I want to take this opportunity to thank you and the other members of this subcommittee for your leading role in last year's historic increase in NIH funding. The strong bipartisan support for NIH exhibited last year provides renewed hope for those of us struggling with chronic disease on a daily basis.

Founded nearly 30 years ago by parents of children with diabetes, JDF is a voluntary health agency dedicated to finding a cure for diabetes through the support of research. JDF gives more money to diabetes research than any other nonprofit, non-governmental organization in the world. This year, the Foundation expects to commit nearly $65 million directly to diabetes research.

Diabetes is an insidious disease, and remains widely misunderstood by the general public. Insulin is not a cure for diabetes, it is merely life support. Diabetes is the leading cause of new adult blindness, kidney disease, and non-traumatic amputations, costing this country nearly $100 billion annually. Sixteen million Americans suffer from diabetes. On average, a person with diabetes can expect to live 15 fewer years than someone who does not have the disease. In addition, it is one of the most common chronic diseases affecting children, a group upon which it has an especially devastating impact.

Before discussing the exciting potential of stem cell research, allow me to speak briefly as a parent. The daily regimen of Sam's blood checks and insulin injections (up to 5 per day) are coupled with our need to balancing his diet and exercise: a serious challenge in dealing with a 7-year-old soccer player. The medical troubles

for Sam are compounded by the vigilance and worry that extract a heavy toll on the rest of the family. For example, my wife is regularly up in the late hours of the night doing blood checks while Sam sleeps: we wonder is his blood sugar too low? Will he find the middle ground between a "low" or coma and being too "high" in the morning? I can't recall a night since Sam was diagnosed when we slept peacefully, free of the worry that the balance between his food, insulin and exercise was not good enough. I'm unwilling to accept the enormity of this medical and psychological burden and I am personally devoted to bringing it to an end for Sam and all type I diabetics. I implore you to continue to make it possible to cure diabetes, for diabetics and their families.

Human Stem Cell Research: A Potential Cure for Diabetes

I would like to commend the Subcommittee for holding these important hearings on stem cell research. The recent discoveries in the field hold the potential to end all of this and finally find a cure for diabetes.

Based on these discoveries, it is now foreseeable that human stem cells could be stimulated to develop into pancreatic islet cells to replace those that have been destroyed in individuals with Type 1 diabetes. Stem cells have the potential to develop into any tissue or organ in the body and yet cannot develop into a full human being. Moreover, these cells could be engineered in such a way that people who receive them might not need highly toxic immunosuppressive drugs, which prevent the body from rejecting "foreign" tissue—currently a major obstacle to successful islet transplantation.

One of the most promising ways of curing diabetes is to restore biologically the function of islet cells. This could occur either through islet cell transplantation or through engineering of cells to restore the insulin-secreting function. In both instances, the availability of stem cells would significantly expedite research progress.

Islet cell transplantation has been largely unsuccessful for two important reasons:

—Insufficient islets available for transplantation; and

—Recurrence of the autoimmune response that attacks the islets after transplantation.

The problem of insufficient supply of islet cells could potentially be solved through additional stem cell research. Because the cells being studied are so early in their developmental stage, we are hopeful that we will be able to one day direct their development into any human tissue or organ. If and when scientists can specialize these cells to become insulin-producing islet cells, cell lines could be developed to produce an unlimited number of islet cells. This would effectively solve the islet cell supply problem.

In addition, in most cases, the immune system of a person with Type 1 diabetes will not tolerate an islet cell transplantation, even when an individual is given anti-rejection medications (which themselves can cause serious problems). Because stem cells are primordial all-purpose cells from which all tissues of the body develop, it may be possible to alter them genetically so that they will not be susceptible to an immune attack. This would negate the need for immunosuppression.

Ethical considerations

JDF understands that stem cell research raises important ethical considerations that need to be addressed. However, we feel that appropriate safeguards can and should be established to ensure that this important research can be conducted using federal funding.

The 1994 Human Embryo Research Panel, which included scientists and ethicists, studied the ethical issues raised by this type of research and concluded that stem cell research involving "preimplantation" human embryos is acceptable for federal funding. We believe that the Panel's report provides a scientific and ethical basis to justify federal funding for human stem cell research. This report could also serve as the basis for the establishment of a set of safeguards to ensure such research is conducted ethically, in both public and private settings, while still allowing for significant advances in the fight to cure diabetes.

Summary

Mr. Chairman, the opportunities presented by human stem cell research offer us the promise of significant advances—and perhaps a cure—for diabetes. A world without diabetes for all of the children and adults who currently suffer from its devastating impact continues to be our goal, and we urge you to ensure that federal policies allow this research to continue to speed our path to cure this disease.

STATEMENT OF RICHARD PIKUNIS, J.D., PARKINSON'S PATIENT, MARLTON, NJ

Senator SPECTER. We now turn to Mr. Richard Pikunis, also a lawyer and a doctor, J.D., diagnosed with Parkinson's disease 3 years ago at the age of 27, having exhibited symptoms since the age of 24. He persevered and received his law degree in May of last year at Widener University School of Law. He lives in Marlton, NJ, a suburb of Philadelphia, if I may say. Many of us consider Marltons Philadelphians. [Laughter.]

He has one child and one on the way, and is anxiously awaiting a resolution of the political issues for medical research on Parkinson's.

We welcome you here today and look forward to your testimony.

Mr. PIKUNIS. Thank you, sir. My name is Richard Pikunis. I wish to thank Senator Specter and the other members of this committee for allowing me the opportunity to discuss my experiences with Parkinson's disease with you.

I am not a scientist, nor do I hold myself out as an expert in the field of stem cell and fetal tissue research. What I can share with you today is my perspective as a young person with the terrible debilitating disease known as Parkinson's.

Parkinson's disease is a progressive neurological disorder caused by the degeneration of brain cells that produce dopamine, a neurochemical that controls motor function. By the time symptoms of stiffness, tremor, and slowness of movement begin to exhibit themselves, the brain has already lost about 80 percent of its dopamine-producing cells.

Of course, I did not know any of this for a long time. Dopamine meant as much to me as planning for my retirement, and science had no bearing on my life. However, today I look to science praying it will be able to save my life.

When I was 24 years old, my symptoms were apparent, but because of my age and general overall good health it went undiagnosed. I had the symptoms associated with a typical Parkinson's patient, slowness and loss of movement, postural instability, resulting in frequent falls, a distorted gait and muscle rigidity. I remember not going on a family vacation because my body ached so bad, I was so stiff and rigid, that walking consumed all my energy.

Because of a common misconception that Parkinson's diseases is a geriatric disorder, the diagnosis was not as obvious as it should have been. Besides, I do not exhibit the most prominent telltale symptom of Parkinson's, the tremor. In fact, according to the American Parkinson's Disease Association, tremors only occur in about 70 percent of patients, and it is usually these tremors that bring a patient to the doctor.

However, after years of knowing something was wrong, but not quite able to put my finger on it, my mind was finally put at ease when the doctor told me I had Parkinson's. Yes, at the ripe old age of 27 years, and after three medical opinions, it was conclusive. I did have Parkinson's disease.

I was just starting out in life, the same age as my friends who were getting married and buying houses. They were enjoying life, as I felt life was slowly being drained from my body.

Not knowing what Parkinson's was was probably why I was not as upset as my parents upon hearing the diagnosis. I remember my mother abruptly leaving the doctor's office, only to find her moments later in the car sobbing.

Since then, I have learned a lot about Parkinson's, and I am here to tell you that I hate it with a passion. Parkinson's has robbed me of my youth. Parkinson's has been there for every major event of my adult life, and overshadows everything I do, and fights me every chance it gets. Parkinson's walked down the aisle with me at my wedding. It made my life hell as I attended law school. As if the stress of law school was not bad enough, I had to constantly be reminded by my stiff, aching body that Parkinson's was still with me.

I had always hoped to have a career in Federal law enforcement when I graduated from law school, but now I am finding it difficult to even enjoy a walk with my family.

I can accept all this, but what scares me the most about Parkinson's disease is that it holds my future in its hands. My son celebrated his first birthday and is learning to walk as I am slowly losing my ability to do so. I wake up every morning barely able to move until my medication kicks in.

I am currently taking L-dopa to replace the dopamine that my body can no longer produce, but it is becoming less effective at the current dosage. I know L-dopa will not be able to adequately treat my symptoms forever, and it really scares me when I think about how my life will be in a few years if we do not find a better treatment or a cure for Parkinson's. I wonder if I will be able to teach my children how to ride a bike, or dance at their weddings.

I am scared about forced retirement before I am financially stable. I just graduated from law school. Believe me, I cannot afford not to work, but I know the choice may not be mine to make, because with an increase in L-dopa comes the debilitating side effects such as involuntary body movements and motor fluctuations. Sometimes these side effects are just as bad as the disease.

It is imperative that now, right now, we expand the research into Parkinson's diseases. Preliminary scientific evidence indicates investment in Parkinson's research, into areas involving stem cells and fetal tissue, have the potential to produce viable treatments and cures not only for Parkinson's disease but for heart failure, diabetes, stroke, Alzheimer's, and spinal cord injuries, to name a few.

Researchers are on the cutting edge of discoveries that will change immeasurably the lives of millions. Please make it possible for the scientific community to explore these avenues of research. Congress has taken steps in the right direction, the enactment of the Morris K. Udall Parkinson's Research Act, but my Government is still falling short in the eyes of millions who desperately need their help.

We want the money authorized by the Udall act to actually be spent on research. Start investing the millions it will take to cure us rather than the billions to care for us. Please help me and others like me live our dreams and maintain our dignity.

PREPARED STATEMENT

Only you can help put an end to the human suffering associated with Parkinson's disease. Do not let me become a burden to my loved ones and society. Let me live my dream of an optimistic future with my wife and family.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION (BIO)

EXECUTIVE SUMMARY

Pluripotent stem cells research provides the hope of a new generation of therapeutics. Using cell transplants instead of drugs, biologics and other current therapies, provides new hope for patients with cancer, spinal cord injury, stroke and degenerative diseases. As the federal government has not to date provided funding for pluripotent stem cell research, the biotechnology industry has taken the lead in funding it. For industry to continue to fund this research, and for this research to be developed into products at the bedside for patients, patent protection must be available. For the vital partnership between industry and academic biomedical researchers to remain strong, the terms of technology transfer agreements must be commercially reasonable.

STATEMENT

The Biotechnology Industry Organization (BIO) represents 832 companies, state and affiliated organizations engaged in biotechnology research on medicines, diagnostics, agriculture, pollution control and industrial applications. BIO appreciates the leadership of the Subcommittee in providing strong support for research on pluripotent stem cells and for this opportunity to participate in this hearing.

Pluripotent stem cell research is a very exciting, cutting-edge area of scientific research whose promise has captured the imagination of the research community, patient advocates, and the American public. We urge the Subcommittee to continue to lead the way in supporting this research and the policies that will speed it to market for the benefit of patients.

Over the last 50 years, the only constant in medical innovation has been that scientists are constantly trying to treat human diseases through new approaches. The newest approach which we are here today to discuss is using embryonic or pluripotent stem cells (early human cells) to treat degenerative cell based diseases. (We have attached to the end of this document two figures to help explain stem cells' place in embryonic development and the new method of generating these cells). Stem cell research is intended to find treatments which do not depend on chemical compounds, rather they use living cells as the treatment or cure.

It is anticipated that these cells will be differentiated into blood, skin, heart, or brain cells and may be able to treat cancers, spinal cord injuries, heart disease and potentially many other diseases.

The science of stem cells

There are 200 different kinds of cells that make up most of the human body. These cells are differentiated, which mean that they have a distinct morphology (shape and size), and have achieved a specialized function such as carrying oxygen or transmitting "nerve" signals. For years scientists have known about "blood stem cells" (cells that can become one of several different blood cells such as white blood cells or red blood cells) and the potential uses of umbilical cord blood.

However, late last year the Geron Corporation announced that its research had, for the first time, successfully derived human embryonic stem (ES) cells and maintained them in tissue culture. This was a great step forward in this area of research.

Stem cells are the earliest precursor of human differentiated cells. These cells come from an embryo, and, therefore, have been defined as embryonic stem cells (ES). These cells, ES cells, have the capacity to become virtually any cell or tissue in the body. These cells are "pluripotential"—that is these cells can be used to form almost any tissue. These cultured ES cells are special as they have the capacity for self-renewal, meaning they can produce more of themselves without limit.

The excitement in the research and patient community is understandable. There are two ways that ES cells are an advancement: first, as a research tool to study developmental biology; and second, as the starting point for therapies to create cures to some of the most deadly diseases. The excitement and promise of this ad-

vancement is seen in the letter that 52 patient and medical professional societies sent to Members of the Senate on December 2, 1998, which supported stem cell research and development (letter attached).

Although many see the benefits of stem cell research, we understand that for some people this new area of research raises ethical issues. These issues range from the ethics of conducting research on human fertilized eggs to patenting research procedures.

Stem cell research

In compliance with current law requirements and concerns of the public and the use of public funds to support research projects that raise ethical concerns, the federal government has not sponsored research to derive pluripotent stem cells. Now that these stem cells have been derived, the government is determining whether it can and should fund research on these cell lines.

Recent studies have documented that government funded basic research is an important precursor to innovation by the biopharmaceutical industry.[1] In addition, public funding stimulates additional investment by the drug companies and enhances the effectiveness of their Research and Development expenditures as well.[2] According to a study of connections between pharmaceutical firms and publicly funded scientists in academia and government, these relationships have a large impact, raising the level of private sector research productivity by as much as 30–40 percent.[3] (See "Federal Funding for Biomedical and Related Life Sciences Research, fiscal year 1999," by Federation of American Societies for Experimental Biology.) In addition, research that is funded by the Federal government is subject to a variety of oversight mechanisms.

Technology partnership mechanisms

Technology transfer is a process by which amorphous areas of scientific research are defined (generally through patents), then sold or licensed to others. This process promotes the commercial development of products as it is designed to provide for the capturing of the value of basic research by the basic researcher (generally a nonprofit university researcher), and the shifting of the research to organizations that are better able to assume the financial risk associated with developing a commercial product (generally a corporation).

In biotechnology, technology partnerships take a number of forms depending on whether they involve the NIH, NIH-funded research, or in the case of stem cell research, non-government support of research. In each case the biotechnology industry pays royalties for the patent rights to medical technologies. For your information, the principal technology partnership mechanisms are listed below:

Cooperative Research and Development Agreement (CRADA).—A CRADA is an agreement through which researchers at the NIH and private companies negotiate terms for cooperative research and define the rights of the parties to use licenses for any patents which might be created as a result of the research. CRADAs are the cornerstone of the basic biomedical research partnerships between the NIH and the biotechnology and pharmaceutical industries. In many cases the corporate partner provides funding and other resources to conduct research at the NIH. This corporate partner will then take the new technology and develop a marketable product.

Bayh-Dole agreements.—Bayh-Dole Agreements are agreements between universities or medical institutes and biotechnology companies or pharmaceutical companies in which the parties define the licensing rights to patents and agree on how to share funds and materials. Similar agreements exist between intramural government researchers and licensees.

Technology licensing.—In the absence of federal funds, organizations are free to license technology as they see fit, without oversight of any Federal office. This freedom to license insures that research organizations are able to capture the value of the research. Generally these agreements are in accord with the mission of the organizations involved. Anti-trust considerations sometimes play a role.

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[1] Andrew A. Toole, "The Impact of Federally Funded Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry," Madison, Wisconsin: Lauritis R. Christensen Associates (1997).

[2] Andrew A. Toole, "Public Research, Public Regulation, and Expected Profitability: The Determination of Pharmaceutical Research and Development Investment," Madison, Wisconsin: Lauritis R. Christensen Associates (1997).

[3] Iain Cockburn and Rebecca Henderson, "Public-private interaction and the productivity of pharmaceutical research," National Bureau of Economic Research (1997).

Licensing of patents

The partnerships that are formed are based upon the licensing of patents to basic biomedical research discoveries. These licenses are critical to the relationship between biotechnology and pharmaceutical companies and their research partners. Without patents to protect the taking of an invention by a competitor, a company cannot justify its research investment. For instance, any company would be competitively disadvantaged by investing in stem cell research if other companies could freely acquire it. It is crucial that the basic research institution secures patents on their inventions so companies that invest money in developing these inventions can benefit from their investment. These licenses generally require companies to make royalty payments to the proprietary owner of the license, or licensor, based on any sales of products attributed to the licensed patent. These arrangements allow the research organization to gain a benefit from the research while not bearing the risk associated with the continued and expensive research and development program. While protecting investment and rewarding risk-taking, patents also act as a powerful spur to competitors to improve on the patented technology or provide alternatives.

In this regard, the biotechnology industry anticipates the assumption of the risk and hopes to pay royalties as a part of a license agreement. Companies frequently license technology from one another and the norm is to include royalty payments. Restrictive future licensing provisions will merely diminish the value of the licensed technology. Logically, in some cases, restrictive practices would prevent the licensing of some technology and thereby prevent its development.

Patents and stem cells

Prior to the licensing of technology, the nebulous boundaries of a technology must be defined so that the intangible assets can be handled by the U.S. business and our legal system. In general that is done through the patent system. A U.S. patent is defined by claims that provide sharply defined borders to technology. These boundaries give clear notice to others so that the area can be avoided or licenses can be taken to practice what is defined. The claims can be directed to products and compositions of matter. Once boundaries are established and claims granted in an exciting field such as stem cells, patents provide a powerful stimulus to competitive academic groups and companies to improve on technologies and/or find new routes to achieve the same effects. In this way, patents increase the range of effective products available to treat intractable diseases and improve social welfare.

There may be no industry which is more sensitive to patent protection than the biotechnology industry. The rate of investment in research and development in this industry is higher than in any other industry. Any law which undermines the ability of biotechnology companies to secure patent protection undermines funding for research on deadly, disabling and costly diseases. Capital will not be invested in biotechnology companies if they are not able to secure intellectual property protection to recoup the substantial investments they must make in developing a product for market.

Our industry's position on patents follows from one simple fact about the biotechnology industry; most of our firms fund research on deadly and disabling diseases from equity capital, not revenue from product sales. Without investors taking the risk of buying the stock of our companies, much of our vital research would end. Almost without exception our industry cannot borrow capital. Our principal, and for most of us, our only source of capital, is equity capital.

Intellectual property protection is critical to the ability of the biotechnology industry to secure funding for research because it assures investors in the technology that they will have the first opportunity to profit from their investment. Without adequate protection for biotechnology inventions, investors will not provide capital to fund research. There is substantial risk and expense associated with biotechnology research and investors need to know that the inventions of our companies cannot be pirated by their competitors.

Our industry's general position on patents is identical to our industry's position on stem cell patents. In regard to stem cell research, patents are vital and they should be freely transferable. These patents are essential to the continuation of stem cell research. No money has yet been made from selling stem cell products. It is unreasonable to expect any money to be made for many years to come from this research.

Research exemptions

This position is entirely consistent with the continued existence of a "research exemption"[4]. (This exemption is different from the statutory Bolar[5] exemption that provides additional protections for non-patent holders. Bolar is not relevant to stem cell research at this time as no therapeutics are nearing submission for regulatory approval). The courts and BIO recognize that it is important that patents do not block academic research that move a field forward and which do not compete in the marketplace. Accordingly, the courts have created the "research exemption" as a defense against patent infringement for academic research—the type of research typically done by universities. The biotechnology industry supports this exemption. The industry benefits from the knowledge that is created by the research being done on technology that the industry has patented. This judicially created doctrine and the support of the doctrine from the biotechnology industry has in having no biotechnology company ever suing a university for performing academic research on patented technology.

In large part due to the patentability of new areas of research like stem cell research and the transferability of patents, the United States leads the world in biomedical research. The competitiveness of the U.S. biotechnology industry means that the most vulnerable U.S. patients have hope. It means that they can look to American biotech companies to develop the therapies and cures which will ease their suffering.

Summary of Commercial Development Issues Regarding Stem Cell Technology

The partnerships between NIH and NIH-funded grantees and the biotechnology and pharmaceutical industries stand at the center of the world's most productive biomedical research enterprise. Following is a summary of BIO's views on the commercial development issues associated with stem cell and other biomedical research.

—NIH and NIH-grantees have entered into a broad array of research agreements and licenses. These agreements and licenses typically provide that intellectual property generated by NIH and NIH-grantees is licensed or sold to biotechnology and pharmaceutical companies in exchange for royalty payments on any sales.

—Central to these relationships are patents which ensure that the results of the university and industry investments are not misappropriated by those who did not make the investments. Without patent protection no company can persuade its investors to put their capital at risk, and NIH and its grantees would have nothing to license. The patentability of inventions is determined by the Patent and Trademark Office under well established guidelines.

—Universities filed over 3,000 new patent applications in fiscal year 1997 in the expectation that they could generate revenues in the form of licenses and royalties. The availability of patents—which grant an inventor 17 years of protection from competitors—leads to an intense competition in the development of life-saving drugs, biologics and devices. Patients in need of new medicines and devices are the beneficiaries of this competition.

—Patents do not block university researchers from conducting research on patented inventions. These researchers are protected from a patent infringement action by an "experimental use" exemption from an infringement action because they are not competitors with a commercial motivation.

—Licenses can be exclusive or non-exclusive (i.e., sold to one, or more than one entity). Each type of license may be appropriate depending on the circumstances. About 10 percent of NIH's licenses are exclusive. Academic researchers not engaged in research for commercial use are not affected by the existence of an exclusive license. The Association of University Technology Managers (AUTM) Licensing Survey, fiscal year 1997, found that universities executed 2,665 licenses and options of which 1,377 were exclusive (52 percent) and 1,288 were non-exclusive (48 percent); U.S. hospitals and research institutes executed 361 licenses and options, of which 208 were exclusive (58 percent) and 153 were non-exclusive (42 percent); and Canadian institutions executed 198 licenses and options, of which 139 were exclusive (70 percent) and 59 were non-exclusive (30 percent).

—An exclusive license gives a company a greater incentive to invest its resources in the development of technology and this means that the companies are able

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[4] Popenhusen v. Falke, S.D.N.Y. 1861, 19 Fed.Cas. 1048, Northill Co. V. Danforth, D.C.Cal. 1943, 51 F.Supp. 928, Chesterfield v. U.S., 1958, 159 F.Suppl 371, 141 Ct.Cl. 838, Norfin, Inc. v. International Business Mach. Corp. D.C. Colo., 1978, 453 F.Supp. 1072, affirmed 625 F.2d 357, Ares-Serono v. Organon Int. B.V., D.Mass.1994, 862 F.Supp. 603.

[5] Roche v. Bolar Pharmaceutical Co., Fed. Cir 1984, 733 F.2d. 858 and see 35 U.S.C. 271(e).

and willing to pay a higher royalty rate to the NIH or an NIH-grantee. Exclusive licenses are particularly appropriate in cases where substantial risk and expense are involved in the development of basic research into a marketable product.

—In 1997 NIH received approximately $40 million (1,000 licenses) and its grantees approximately $300 million (5,000 licenses) in royalties from its licenses to biotechnology and pharmaceutical companies. This income helps to fund additional research.

—In 1997, of all federally funded grantees, the top ten recipients of royalty income include: University of California System ($67.3 million), Stanford University ($51.7 million), Columbia University ($50.3 million), Florida State University ($29.9 million), Massachusetts Institute of Technology ($21.2 million), Michigan State University ($18.3 million), University of Florida ($18.2 million), W.A.R.F/University of Wisconsin-Madison ($17.2 million), Harvard University ($16.5 million), Carnegie Mellon University ($13.4 million). This income helps to fund additional research.

—In 1996, separate from licensing royalties, industry sponsored $1.5 billion in research at U.S. universities, hospitals and research institutes, the overwhelming portion of which is in biomedical research (such as conducting clinical trials, including $41 million at Massachusetts General Hospital and $26 million at the Mayo Clinic). This income is vital to the biomedical research efforts of these institutions.

—From 1980 through 1997 these technology partnerships between federal government agencies and university-based research were reported (many aren't reported) to have led to the founding of 1,521 U.S. companies.

—These technology partnerships, and the patents on which they are based, are particularly important to small biotechnology companies. These companies tend to focus their research on breakthrough technologies that come from basic biomedical research. They also must have strong patent protection to justify the risks they take. Most of these companies have no revenue from product sales to fund research, thus, they depend on venture capital and public market investors. In 1997, the biotechnology industry lost $4.1 billion. Previous years have had similar financial losses (1996, $4.5 billion loss; 1995, $4.6 billion loss; 1994, $4.2 billion loss). The biotech industry hasn't ever had a profitable year.

Conclusion

BIO appreciates the opportunity to present these views on this important issue. We look forward to working with the Subcommittee to support policies that will speed the development of pluripotent stem cell research into products for the benefit of patients.

OBTAINING BY ETHICAL MEANS

Senator SPECTER. Thank you very much, Mr. Pikunis, for that very moving statement, and we will start now 5-minute rounds of questioning.

Your testimony goes to the point that I made in my opening about the sense of urgency. There appears to be a ban—Senator Harkin may be right that there really is no ban, but NIH is treating it as a ban, and instead of importuning interpretation and litigation we have the way to resolve it with legislation that came out of this subcommittee.

The purported ban, we can lift that ban, and when you talk about your personal situation, that is precisely the sense of urgency which I think ought to move the Congress to get this done.

Let me ask you the first question, Dr. Goldstein. Picking up on your statement about obtaining by ethical means, the embryo is a sperm-fertilized egg and will grow into a fetus upon implantation in the uterus.

What we have here are discarded embryos, so there is no possibility of the embryos which are used for stem cell research to be implanted and to produce a person, is that a correct scientific statement?

Dr. GOLDSTEIN. Yes; that is our understanding of the situation, Senator. In addition, we presume—I presume personally these embryos may be damaged in handling. You may not want to implant them into women. Actually, to implant them would itself be unethical.

Senator SPECTER. The long and short of it is that it is ethical to take these discarded embryos, which are not going to be used for implantation, to produce a human being for medical research?

Dr. GOLDSTEIN. Yes; we believe so.

Senator SPECTER. I want to turn to you, Mr. Dickinson, on the question of patent applicability, and again I am sorry that Geron is not here to give us their view of the issue.

If the stem cell is defined as an end product, then it is subject to patent protection, but if it is considered to be a research tool, then in that situation—or is there any other interpretation where it would not be subject to patent protection?

Mr. DICKINSON. Senator, patent claims are a very arcane and very semantic type of——

Senator SPECTER. That is why we have you here.

Mr. DICKINSON. Thank you. I think it would be not appropriate necessarily for me to comment on or speculate on what the breath of a claim might look like that we do not have before us at this time.

The claims that are directed to stem cells, as you point out, are directed to stem cells which have been isolated and purified and, as such, from a long line of case law are subject to patent protection.

Senator SPECTER. Well, if they are a research tool are they subject to patent protection?

Mr. DICKINSON. They can be, yes.

Senator SPECTER. Under what circumstance might they not be?

Mr. DICKINSON. We have a four-part test, as I mentioned, for patentability, and if they are outside that test—for example, if they are not subject matter which is patentable by statute, which is a very broad statute, or if they are not new, if they have been known before, or if they are obvious in view of what has been known before, they would not be patentable.

Senator SPECTER. So we might have to change the law to move them outside of patent protection?

Mr. DICKINSON. That is always a possibility, Senator.

Senator SPECTER. Well, Congress can do that.

Mr. DICKINSON. Yes, sir.

Senator SPECTER. Dr. Freire, the patent contains 11 claims, some of which use the term, primate to identify the Wisconsin work. Primate might be construed as to cover humans, although the term is not—the term human is not presented among the claims. Could that be interpreted to have any implication for producing human stem cells?

Dr. FREIRE. Yes, Senator. We checked with the holder of the patent and they told us that they have prosecuted the patent to include humans, although none of the research supported by NIH was for humans. It was all for the monkeys.

Senator SPECTER. Does that bear upon the issue of human cloning?

Dr. FREIRE. Well, the claims as they are right now on stem cells and their production are from primates. As you point out and, as such, humans are primates.

Senator SPECTER. My red light is on. I will pick up on my first question to Dr. Melton in my next round.

Senator Harkin.

PATENTABILITY OF RESEARCH TOOLS

Senator HARKIN. Thank you, Mr. Chairman. My first question would be to you, Dr. Freire. You mentioned, and I caught it when I sat down here when I came in a little bit late, a dilemma. Would you expand upon what you meant by that dilemma?

Dr. FREIRE. Yes; it actually bears on the question that Senator Specter asked Mr. Dickinson, whether or not research tools are patentable. They are, indeed, patentable, so the question is, how do you enforce those patent rights? We are very respectful of the patent holder's right to extract value from his or her invention. The concern arises when the value is extracted, from our perspective, at a very early stage, at the research stage, as we are being asked to do at this point. The patent, of course, as Mr. Dickinson pointed out, allows for the making, using, or selling, precluding others from making, using, or selling, and our scientists are making and using many of these research tools.

When obligation is tied to these very early discoveries by the patent holder, at the end of the day we have a very encumbered potential drug or therapeutic that may never see the market because of these very complicated obligations.

On the other hand, it is of value to the owner of the patent, and we certainly cannot diminish that value. We have learned very many lessons from the 20 years. Your recollection on Bayh-Dole is exactly correct. It was an economic development effort. But one of the lessons we have learned is that while we grant that protection we should be able to separate the way we license this technology to ensure that the rights to maintain unencumbered research continue while we extract the value for the commercial partner. That was not something we thought about doing early on.

BAYH-DOLE ACT

Senator SPECTER. Under Bayh-Dole, if the Federal Government is involved in any of the funding for the basic research, as I understand it—correct me if I am wrong—the Federal Government, NIH, retains the right to use those findings. Even though they are patentable and patented, they are able to use those as research tools intramurally.

Dr. FREIRE. Well, we actually retain the right to use—we have a royalty-free right to use the patent. We have a license to all of those patents for Government purposes, that is, the intramural scientists at NIH.

Senator HARKIN. A nonexclusive right?

Dr. FREIRE. That is correct.

Senator HARKIN. And it is not—well, it is not something that you pay for, that we pay for. The Government retains that right.

Dr. FREIRE. Correct.

Senator HARKIN. But you can only use that for intramural——

Dr. FREIRE. Or for Government purposes, contractual Government purposes, like if we have a contract and the contractor is doing work for the Government, that is one of the retained rights.

Normally, these Government rights that are retained are not interpreted to ensure to our grantees. Our grantees are not considered part of the Government user rights.

Senator HARKIN. And you think that should be allowed? I mean, you raise that as a problem.

Dr. FREIRE. Yes; I think that we would very much like to see the ability of our funded researchers to use these research tools unencumbered, yes.

Senator HARKIN. And if they use them unencumbered, then let us assume that they find an application—they are able find a means of developing that stem cell into muscle tissue or something, and you get to the Parkinson's Disease, for example, who has the right to that patent?

Dr. FREIRE. Well, the new invention, if it is in fact a new invention, could be patentable by the grantee.

Senator HARKIN. Well, would the grantee then have to pay a licensing fee to the original patent holder of the stem cell?

Dr. FREIRE. Well, what normally happens is, the grantee would license to company X. Company X would have to ensure that they have the rights to practice the invention for commercial purposes. Company X will go back to the companies that hold other rights and establish licensee agreements with the other commercial partners to ensure that they can move forward.

Senator HARKIN. I just want to be clear on this. My time is up. If the Federal Government retains the right to be able to use these research tools as a means of enabling our grantees—say another university—to be able to use these as a research tool, that grantee is not paying any license rights to the initial patent holder, is that correct? That is right.

And then the licensee develops a strain from that, and they then want to patent that strain and obtain the recompense for that. How, then, do we ensure that it gets back to the original patent holder that they also would retain some right in that?

Dr. FREIRE. Well, the original patent holder, if they have a dominant patent, would be approached by the licensee who wants to bring the product to commercialization. Otherwise they would be infringing the patent of the original holder.

Senator HARKIN. I see. They could use the line for any kind of research, but when they take the step to commercialize it, then they have to go back to the original patent holder to obtain some rights?

Dr. FREIRE. Let me clarify, Senator. In the pharmaceutical and biotechnology industry the research exemption really does not exist, per se, which is what you are getting at. We really do not have a very solid research exemption.

Companies have, in fact, come back to the NIH and said, you need to take a license because you are making or using patented technology. But the pharmaceutical and biotechnology industry have worked with the academic sector in a hand-shake type agreement, because they understood the importance of basic science.

But, we are seeing companies come back and exercising their rights this way.

Senator HARKIN. Thank you, Mr. Chairman.

Senator SPECTER. Dr. Melton, you have extraordinary credentials here, with your chairmanship of the Molecular and Cellular Biology Department at Harvard University, and you have equally impressive personal interest with your 7-year-old son.

Tell us what would the key processes be to develop stem cells into cells that produce insulin, or otherwise deal with diabetes?

Stated differently, how close are we to using stem cells to solve the diabetes problem for your son?

Dr. MELTON. That is a very good question, Mr. Chairman. What I can tell you with some confidence is that the work with mouse stem cells is so encouraging that one is within a few years of being able to get those cells, or direct them to become pancreatic cell types in culture, and that is why I think it is so imperative that we immediately begin to transfer that information, to test our knowledge, in the case of the human cells to determine whether there are any significant differences.

I was very encouraged by that questioning, because it is clear that you and Senator Harkin are trying to free up Federal funding so that this sort of research can continue.

Senator SPECTER. Well, as you know, there were many millions of dollars added by this subcommittee last year, but it does not do a whole lot of good if the NIH is barred from using that on this very dramatic breakthrough.

Dr. MELTON. What I can see, speaking from the scientist's point of view in the trenches, is that there are many people with very good ideas, novel ideas about how to actively pursue this research, and we are anxious for Federal funding.

Senator SPECTER. Your few years is very helpful. We do not have a whole lot of time, so I am going to move on to Mr. Pikunis.

On Parkinson's, there have been very effective advocacy groups. With the Udall legislation last year, that sort of took the Congress by storm on the difficult matter of having Congress establish priorities, which are characteristically left for NIH.

Just how pressing is it for you personally, Mr. Pikunis, in terms of your daily activities, to have the assurance that NIH will move forward, the Federal Government will move forward? How does that impact on your daily life?

Mr. PIKUNIS. I think it is very important, because right now under current medication-type treatments for Parkinson's Disease I am fine as long as I am on the medication, but I notice if the dosage goes too high I start exhibiting the side effects of the involuntary body movements, and that is at a slightly increased dose from what I am on now.

As long as I am on the current dose, I am fine, but I know that the current does is not going to last me forever.

Senator SPECTER. Dr. Goldstein, you identified a range of other ailments in your testimony, heart disease, Alzheimer's—does this have application for cancer as well?

Dr. GOLDSTEIN. Yes; we believe it does. Many of the therapies that are involved in cancer chemotherapy wipe out many types of cells in the body that need to be replenished. Often, they are done

by bone marrow transplants. Stem cells could, in fact, be a much better source of these vital cells.

Senator SPECTER. Dr. Melton gives us a few years, as he says, with respect to diabetes. Would you give us a ball park figure with respect to Alzheimer's?

Dr. GOLDSTEIN. Alzheimer's is a very tough problem, Senator, and I do not think we have a very good sense of how long it will be. I guarantee you that every day we delay is another day that the clock ticks and we are not making progress using this vital research need.

Senator SPECTER. People in Congress like to have figures, even ball park figures. Let me press you on the question, and very seriously, this business of advocacy is a very tough issue.

The first thing we have to do is disabuse many of the notions that using embryos is somehow related to destroying human lives. That is a very, very big political issue, and you, ladies and gentlemen, a pretty good-sized group here, ought to be aware of that in terms of your advocacy. You have got to approach a lot of people to disabuse that notion.

And then if you talk in terms of being close, and what the dollars will do, then you start to create an impetus for it, so I want to give you just a little insight into advocacy.

My red light is on, but yours is, and for a very short answer, how long?

Dr. GOLDSTEIN. Maybe 5 to 10 years, Senator, where we could see some hope. We can turn these cells into neurons now, but the question is whether we can turn them into the right sorts of neurons.

Senator SPECTER. Senator Harkin, as is not unusual, has the last word. [Laughter.]

UNIVERSITY OF WISCONSIN RESEARCH

Senator HARKIN. Again, Dr. Freire, in your testimony you mentioned that because the Government funded earlier research on rhesus monkeys at the University of Wisconsin the Government has a "nonexclusive royalty-free right to use the patented cells by or on behalf of the Government." Do those patented cells include human embryonic stem cells?

Dr. FREIRE. The owner of the patent would argue that they do include human embryonic stem cells.

Senator HARKIN. The owner of the patent?

Dr. FREIRE. Wisconsin.

Senator HARKIN. That they do?

Dr. FREIRE. Yes; that the claims to that patent do include human embryonic stem cells. The word human does not appear in the claims. The word primate appears in the claim, and primate encompasses humans. That is the way the owner of the patent prosecuted this application, from what we have been able to discuss with them.

Senator HARKIN. Do you agree with that?

Dr. FREIRE. Yes.

Senator HARKIN. Mr. Dickinson, some in the research community argue the Patent Office is issuing biotechnology patents that are too broad. What is your response to that?

Mr. DICKINSON. Well, the matter of the breadth or the narrowness of the claim is a matter, again, of matching it up against those four statutory requirements that I mentioned.

It has been my experience that when patents issue of a certain breadth in a new technology there is often concern about that breadth, but what happens in reality is that additional patents, what may be called a genus patent, what often happens, very quickly, is the people develop species patents, new and not obvious claims in new patents that would be patentable over that original broad patent.

This is something we have dealt with historically. It has been dealt with effectively.

Senator HARKIN. You do not think they are too broad?

Mr. DICKINSON. Not in general, no. The nature of the breadth of a patent is measured by the prior art.

BAYH-DOLE

Senator HARKIN. My time is up. One final question for all of you. Do we need to readdress Bayh-Dole?

I have heard that it has been a success, but like anything that is 18 or 19 years old, it may need to be readdressed. Do we need to make some changes, because the biotech industry had not really started—it was in its embryonic stage when we passed Bayh-Dole.

Do we need to make any changes in Bayh-Dole, Dr. Freire?

Dr. FREIRE. When I discuss this with my colleagues at universities the president of the Association of University Technology Managers Karen Hersey said publicly that perhaps 20 years later we could go back and look and see how some of these things have worked, so it would not be a full rewriting but an assessment. I think it would be responsible to take a look at what those items are.

Senator HARKIN. Well, I for one, just speaking as an individual, am open to any suggestion from you or anyone else in the audience about suggestions for modifications if modification is needed. I have not made that decision yet.

Mr. Dickinson, what say you?

Mr. DICKINSON. I am not an expert on the Bayh-Dole Act. It is probably not my place to comment on whether it is working or not.

Senator HARKIN. Dr. Goldstein, how about you? What do you say?

Dr. GOLDSTEIN. I am sorry, Senator, I am not a lawyer, but I can certainly point out that it is always worthwhile reviewing past actions after 20 years have passed.

Senator HARKIN. Dr. Melton, do you have any views on that?

Dr. MELTON. I agree with Mr. Goldstein that the rapid changes in the biotech industry were not foreseen when that act was constructed and I think it is worth revisiting it.

Senator HARKIN. Mr. Pikunis, do you have any views on this?

Mr. PIKUNIS. No, sir; I do not.

Senator HARKIN. I am just trying to figure out—and again, the dilemma is, we want the research, we want the money invested, we want private moneys invested, and we also want to make sure that they are able to get a return on that investment and that they are able to patent it, but we also want to make sure the research is

broadly and widely available to others, and that we are not hindered by a broad patent that is issued that hinders further research that may be utilized. That is the dilemma.

But I do not know what we will do on the Bayh-Dole Act, Mr. Chairman. I do not know if it needs to be looked at or not. Like I say, I have personally made no decision on that.

Senator SPECTER. Senator Harkin, it may be we will have to take a look at it, and we will have to take a look at the patent laws, or it may be that if Congress takes a look at the patent laws in the Judiciary Committee, that there will be a little more generosity on licensing, and having research going forward. You never can tell how those issues are going to interact.

SUBCOMMITTEE RECESS

Thank you all very much for being here, that concludes our hearing. The subcommitee will stand in recess subject to the call of the Chair.

[Whereupon, at 10 a.m., Tuesday, January 12, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

STEM CELL RESEARCH: HHS LEGAL RULING

TUESDAY, JANUARY 26, 1999

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

The subcommittee met at 9:03 a.m., in room SD–138, Dirksen Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter, Harkin, and Hollings.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENTS OF:

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

HARRIET RABB, J.D., GENERAL COUNSEL, DEPARTMENT OF HEALTH AND HUMAN SERVICES

NONDEPARTMENTAL WITNESSES

STATEMENTS OF:

ERIC M. MESLIN, Ph.D., EXECUTIVE DIRECTOR, NATIONAL BIOETHICS ADVISORY COMMISSION

RICHARD M. DOERFLINGER, ASSOCIATE DIRECTOR FOR POLICY DEVELOPMENT, SECRETARIAT FOR PRO-LIFE ACTIVITIES, NATIONAL CONFERENCE OF CATHOLIC BISHOPS

OPENING REMARKS OF SENATOR SPECTER

Senator SPECTER. Good morning, ladies and gentlemen. The Subcommittee on Labor, Health and Human Services will proceed.

We have scheduled this hearing on stem cells, which is the third in reasonably rapid succession, given the hearing schedules of the subcommittee, this subcommittee or any subcommittee, because of the importance of stem cells research, where there is such enormous potential for medical advances.

The request has been made that the subcommittee not proceed to initiate legislation on the subject because that might complicate the use of stem cells under an opinion which has just been rendered by legal counsel for the Department of Health and Human Services, and we want to work with HHS and NIH to see to it that the most appropriate course is followed here.

The definition of ''organisms'' and ''stem cells'' and the entire medical lexicon is extraordinarily complicated. We have noted that

NIH researchers will only be allowed to work on stem cells obtained by private sources. No NIH-supported researchers will be allowed to conduct direct work on a human embryo, even to obtain stem cells, consistent with the existing ban.

That is an advance, but it is limited, obviously, on the face. There are a series of NIH caveats in that NIH will not fund any human cell research until such time as special guidelines are developed addressing relevant ethical and moral issues. So that is a constraint.

NIH plans to convene a special oversight group to review all research grant applications involving human stem cells in addition to the regular scientific review process, which is another limitation. NIH has asked the National Bioethics Advisory Board for additional guidance.

I appreciate the thinking of NIH on all these very complex subjects. The hearing today will focus on to what extent that may delay research, and there is a question as to whether additional legislation is needed, which we will be addressing. These are very, very difficult legal problems, and that only begins to scratch the surface of the ethical problems which underlie them.

The question is in my mind as to whether legislation is necessary or desirable. Maybe we should not have any legislation. My preliminary thinking is, as I expressed it in the second hearing, after studying the issue from our initial hearing, was that we really ought to utilize this kind of research, and if it requires legislative change then I think we ought to proceed in an expeditious way, but in a careful way.

So Dr. Varmus, that is a very, very brief outline of some of the problems running through my thinking on it. We welcome you here again today. I know that there are scheduling problems among the panel and there is a scheduling problem with the subcommittee. We have advanced the hearing, as you know, to 9 o'clock because we have a caucus on the impeachment case, which is very time-consuming. But it is my firm view that we ought to be taking care of other problems as well. So whatever time we have to meet to do that, however, we can proceed in an appropriate but expedited fashion, we intend to do that. I know you are experienced at that, Dr. Varmus.

We thank you for coming. We compliment you again on the outstanding work you have done at NIH over the years. We have put the government's money where our praise is, to paraphrase a famous statement. The floor is yours, Dr. Varmus.

SUMMARY STATEMENT OF DR. HAROLD VARMUS

Dr. VARMUS. Mr. Chairman, thank you very much.

Senator SPECTER. I would like you to limit the opening statements to 5 minutes, to leave maximum time for questions.

Dr. VARMUS. I appreciate your attention to these issues despite conflicting demands on your time.

My purpose today is threefold. I want to just say a couple of words to remind you about the scientific prospects here, review the legal decision that you have alluded to, and outline the next steps that the NIH proposes to take to pursue our intention to support research with these new stem cells.

I remind you that human pluripotent stem cells were recently isolated by two methods: first from fetal tissue after elective abortion; and from embryos that were donated after treatment of infertility. Neither of these events were supported with Federal funding.

Now, human pluripotent stem cells can divide in culture for long periods. That is part of their usefulness—good morning, Senator—and they have the potential to form virtually any kind of tissue. The research applications of these cells are various and important. They include attempts to understand human development, efforts to develop drugs and test for drug toxicity in new ways, and the potential for developing cell therapies for many diseases, injuries, and conditions.

We discussed in December at your hearing the issue of Federal support for this science and indeed other kinds of science as well. As you heard from the panelists at that time, there are several advantages to receiving Federal support in this area: the open exchange and the more intense and accountable oversight, the greater number of dollars and the more talent recruited to these problems, and the ultimate goal of faster progress toward public health goals.

We at the NIH respect and recognize many ethical and legal concerns about human pluripotent stem cells and the modes by which they are derived. We are firm in our conviction that Federal funds should not be used for this purpose until both the legal concerns and these ethical concerns have been addressed and many constituencies, including Congress and the public, have been consulted.

As a first step, I asked the General Counsel, Harriet Rabb, who is sitting with me today, for a legal opinion about the Federal funding of research with these cells, distinguishing carefully between the use of the cells and their derivation. In other words, can we support work with the established human pluripotent stem cells in view of the appropriation law that you alluded to that bans the use of Federal funds for embryo research.

The essence of her opinion, which you have been given, is that: first, yes, we can fund work with human pluripotent stem cells derived from nonliving fetuses under the existing statutes that govern fetal tissue research; secondly, that we can fund work with human pluripotent stem cells that are derived from embryos because the cells themselves are not organisms, they cannot become organisms, and hence they are not embryos as defined by law. Indeed, at your December hearing, prompted by Senator Harkin, all witnesses who expressed an opinion agreed with this definition.

Now, under the appropriation law it is also the case that we cannot use these stem cells to make an embryo, for example by somatic cell nuclear transfer, and of course we cannot fund work to derive such cells from embryos, although we can do so from fetal tissue.

I presented these views at a meeting of the National Bioethics Advisory Commission on January 19. That meeting was held on this topic in response to a presidential request that the entire area of stem cells research be reviewed in view of the promises of recent work, because he felt that recent advances had indicated that there was a need to reassess the balance between the ethical concerns about such work and the promise for medical research.

We welcome the review by NBAC. We specifically seek prompt guidance with respect to the ethical considerations that will allow us to carry out appropriate oversight on this research.

What are our next steps? Well, first, as I have made clear on many occasions, no immediate funding is occurring until we have our guidelines and process in place. This has been communicated to all of our investigators, both intramurally and extramurally, through memos and Internet postings and news reports.

Second, I am establishing a working group of my advisory committee to the Director which has ad hoc members from all the relevant specialties. That working group will work with NIH staff to compose guidelines for the conduct of research on these cells. The guidelines will address the work to be done with the cells, how the cells were derived, and how the starting materials were obtained.

There are important frameworks that will make this formulation of guidelines easier. There are Federal rules for work with fetal tissue that will be helpful. Some years ago, in 1994, a human embryo research panel issued recommendations that were extremely thoughtful and will be important guides in the development of guidelines.

Finally, the group will also be consulting with the NBAC, with Congress, with the public. We will be publishing a draft of our guidelines in the Federal Register for comment. We expect to have the guidelines written and presented to the public in the course of the next couple of months. We will then promulgate those guidelines and then, in a manner to be determined by the working group, an oversight group will ensure that all who do this work are actually in compliance with the guidelines.

We expect that the vast majority of applications will be mostly routine. That is, they will be applications to work with the existing cells that have been described and whose provenance is well understood. Any uncertainties will be referred to further public discussion and we will carry out annual reporting to Congress and the public about the status of the science, the number of investigators, and any change proposed for the guidelines.

Before I conclude these remarks, let me just make a personal comment, that since I made my presentation to NBAC last week my staff and I have received many, many, thoughtful, interesting, perplexing questions. Let me just address two of those that I think will help inform our discussion.

First, we have been asked, is not working with these stem cells like using stolen goods because some of them were derived from embryos in that embryo research is forbidden? No, no. It is not illegal to derive human pluripotent stem cells. What is forbidden is the use of Federal funds to derive them from embryos.

In this sense, it is like many legal activities for which Federal funding is not permitted. No Federal funds were used, no laws were broken, in producing these stem cells, and we have determined that no laws would be broken if Federal funds are used to support work with them once they have been derived.

The second question we frequently hear is, will not Federal funding for human pluripotent stem cells create a demand to create additional human embryos? Again the answer is no. There are thousands of embryos, indeed probably tens of thousands of embryos,

that are frozen and discarded in the United States in vitro fertilization clinics each year because they are in excess of the number required for successful treatment of infertility.

In contrast, human pluripotent stem cells derived from very few embryos can be used by many investigators for hundreds of experiments because it is usually possible to keep these cells growing for many generations, that is for many cell doublings.

PREPARED STATEMENT

Furthermore, Federal guidelines that protect against coercion in the procurement of fetal tissue are likely to be emulated in the construction of our guidelines for work with human pluripotent stem cells.

Mr. Chairman, no doubt you and Senator Harkin have other questions. I would be pleased to answer them now. Thank you very much.

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

[The statement follows:]

PREPARED STATEMENT OF HAROLD VARMUS, M.D.

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

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

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

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

The methodologies for deriving human pluripotent stem cells are not really new; pluripotent stem cells have been derived from mice since the early 1980s and, since then, from non-human primates and other animals. The first reports of deriving human pluripotent stem cells were published in November 1998 by Dr. John Gearhart and Dr. James Thomson. Neither of these investigations were supported with DHHS funds, although Dr. Gearhart's work could have been supported with Federal funds, because he and his colleagues derived human pluripotent stem cells from primordial gonadal tissue which was taken from a non-living fetus. Federal laws and regulations already exist that govern research on fetal tissue. Dr. Thomson and his co-workers derived pluripotent stem cells from the blastocyst stage of an

early embryo—the embryos used were donated by couples who were receiving infertility treatment; this derivation of stem cells from the embryo does fall under the ban on Federal funding in the HHS/Labor/Education Appropriations Bill. The pluripotent stem cells derived by each of these means appear to be very similar or identical in structure, function, and potential; but it will take more research to verify this.

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

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

The third and most obvious potential application of these human pluripotent stem cells is to direct the specialization of the cells into cells and tissues that could be transplanted into patients for the purpose of repairing injury and pathological processes. A number of such examples are described in my December testimony, but two are worth mentioning here.

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

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

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

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

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

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

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

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

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

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

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

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

SUMMARY STATEMENT OF HARRIET RABB

Senator SPECTER. Before yielding to my distinguished colleague, we are going to turn to Dr. Rabb. We appreciate your being here, Dr. Rabb. You served as General Counsel for the Department of Health and Human Services since May 1993, a very substantial tenure; former director of clinical education of Columbia Law School, vice dean of the law faculty in 1992. We appreciate your joining us and the floor is yours, Dr. Rabb.

Dr. RABB. Thank you, Senator.

I wanted to spend the time today answering your questions, if I may. You have my legal opinion. It is available to you for any questioning you would like to put to us. I felt we should save the time if you do not mind.

Senator SPECTER. I understand you are waiving your opening statement?

Dr. RABB. If you do not mind.

Senator SPECTER. Okay. Let me turn at this point to my distinguished colleague, Senator Harkin.

REMARKS OF SENATOR TOM HARKIN

Senator HARKIN. Thank you, Mr. Chairman. Again, thanks for holding this follow-up hearing. This is an area that captured my

imagination and I think it is one of the most exciting new realms that we have in science, that just holds so much promise. That is why I am just delighted that we got your decision, Dr. Rabb, on this that this research could proceed apace.

I congratulate you, Dr. Varmus, on setting up the subcommittee to do this in a careful procedural, open way so that the public is aware of what we are doing. There is, as you know, a lot of concern about this. There are ethical considerations. I do not downplay those at all. As I have said before on many occasions, I believe that science, especially in this area, holds so much promise for alleviating human suffering and debilitating disease that we have to move ahead aggressively, although, again as I have said, we have to be careful about the ethical considerations.

I believe that scientists working with ethicists and lawmakers together, getting good public input, I believe we can craft—I believe we have, I believe you have, Dr. Varmus. I think we have a great structure to this.

As I understand it, your guidelines will be out in a couple of months. That was the first question I had, but you answered it. In a couple of months you will have these guidelines ready to go. I assume then that funding could then proceed after that, I would hope.

Dr. VARMUS. We will submit for public comment, Senator. We will submit for public comment, for 30 days of public comment.

Senator HARKIN. I see. I am just wondering. Do you have any idea right now—I am certain requests must be coming in as we sit here.

Dr. VARMUS. Yes, correct.

Senator HARKIN. What sort of backlog do you see out there, requests coming in for this kind of thing?

Dr. VARMUS. Well, I have only indirect information. Recall that there will be three ways at least to support this research. Some investigators already have grants and they may be working in this general area, but want to shift their emphasis to work with human stem cells. There will be others who may want to supplement existing grants by a small research application. Others may want to initiate a new grant. In addition, we have intramural investigators who may be interested.

The only way we have to gauge the level of interest at this point is to ask Doctors Thomson and Gearhart, who have made these cell lines, how many requests they have received. We know they have received on the order of 50 to 100 requests from various investigators for these cells to be worked with. But the investigators have been informed that at this point NIH funding is not to be used until we have our procedures in place. We hope, as I say, that that will be within the next few months.

Senator HARKIN. Well, I appreciate that. Again, I am grateful for your opening statement in terms of addressing head-on this issue of encouraging the creation of embryos. I have heard a lot about that. But as you point out, because of in vitro fertilization we have a lot of those, plus the fact that the cells can continue on. So I do not think there is any problem there at all. I am happy that you addressed that issue.

I just, I guess I have less than a question. I just encourage you, Dr. Varmus—I do not think you need any encouragement in this area, but—to really push ahead in it. I mean, the more reading I do on this—I am not a scientist, but the more reading I do on this, this holds so much promise, and it could be in not too long a time for people suffering from Parkinson's or heart disease, just understanding cancer cell biology for example, things like that, that we just have not had that grasp on right now.

I just again hope that you will proceed apace and keeping in mind the guidelines, the need for public input and openness, ethical guidelines. All that taken into account, I just hope you will do everything you can to get the funding out to the researchers. If we need to do anything here in the subcommittee—I know Senator Specter has gotten us a whole lot more money to put into medical research this year. So if you need any more of that money, we can maybe help out.

I am putting you in a tough spot. But I hope we can get more. We are working together on that. I think the budget from the administration is going to be woefully inadequate to meet the needs that we have out there and I am hopeful that we can get more.

So any information that you have on the need for this for the members and our responsibilities here for funding, I encourage you to let us know.

Dr. VARMUS. I will do that, Senator. Thank you.

Senator HARKIN. Thank you, Dr. Varmus.

Thank you, Dr. Rabb, for the issuing of the opinion in a timely manner.

Senator SPECTER. Dr. Varmus, I begin with a baseline question. Just what is the extent of the potential, in your professional opinion, from the stem cells? We have heard very extraordinary comments about potential on Alzheimer's and Parkinson's and diabetes, cancer, heart ailments, a whole range of human medical problems. You are the great expert, Director of NIH. Is that potential accurately stated?

Dr. VARMUS. Well, no doubt, as in all realms of discussion of this topic, there may be some hyperbole. But much of it is in my view accurate. We have experience with similar work done in experimental animals, for example in mice, and we know that it is possible—we have had a long experience now, nearly 18 years or so, working with the parallel types of cells, pluripotent stem cells from mice, and we know that those cells can be induced to differentiate into certain kinds of cells and those cells can be used to replenish diseased or impaired or missing cells in mouse models of disease, that the prospects for repairing damaged hearts and treating congestive heart failure, for example, for returning missing components of the blood system, are all very real.

There will be difficulties in treating more complex diseases, like Alzheimer's. I do not think we should minimize the challenge there. However, in conditions like diabetes, where we know one specific type of cell is missing and that that cell produces a product which circulates in the body, I think the prospects are great.

As I emphasized last time, there are two major impediments to using these cells in cell therapy. One is that we have a still very limited idea of how to take mass cultures of these cells and direct

them efficiently into one cell lineage. But that information will come as we study the way in which these cells undergo their changes in program that allows them to select a cell type to become.

The second problem is one of rejection, histocompatibility, the classic problem in transplantation. We know that those problems may be at different levels of severity with different tissues. We also know that there are ways to manipulate cells in culture to make them seem less foreign to the host.

Furthermore, there are new methodologies that are in development that could obviate these problems in other ways, for example by using our understanding of how cells work and their apparent plasticity to take one kind of cell from the patient himself or herself and to remodel that cell to make it able to replace diseased or absent tissue.

Senator SPECTER. Dr. Varmus, you say that diabetes—you single that out as one which is closer to solution. I know from time to time we press you unduly as to a time frame, maybe not unduly but we press you, because that is a very strong argument with our colleagues to get additional funding if you can put it in a time frame.

Could you give us a ballpark figure as to, say diabetes, when this research might produce the cure?

Dr. VARMUS. Well, as you know, Senator, I tend to be more conservative than some of my colleagues in making these predictions. But in the case of type one diabetes, where we know that replenishment of the beta cell, of the Islets of Langerhans in the pancreas, does have an important positive effect in some patients who have been treated, for example, with pancreatic transplantation.

In that setting, where we know what we need to do, the major challenge is to figure out a way to make a pluripotent cell become a beta cell.

Senator SPECTER. Could you give us a ballpark figure as to how long?

Dr. VARMUS. I would say certainly no sooner than 5 years, but beyond that I am guessing.

Senator SPECTER. Let me ask you now about when these guidelines will be out and when you will be able to start using funds for research. You have a whole series of preliminaries, the special guidelines, the oversight group, additional guidance from the National Bioethics Advisory Board, a comment period.

When? I approach this question with a sense of urgency because, and I do not think it is hyperbole to say, that every day lost human lives are lost. So when?

Dr. VARMUS. I share your concern, Senator. But I do think it is important to have an open and fair process because of the many concerns that are felt and the feeling that the public and Congress want to have a chance to express their opinions.

I am currently assembling the group that will work with us to establish the guidelines. In the case of the existing cell lines, the cell lines that have been made, reported, we know all the details about how the tissues were obtained, I think it is going to be very straightforward. We have a legal opinion, we have the human em-

bryo research panel guidance, we have regulations with regard to fetal tissue research that are very useful.

I believe that in the course of the next couple of months a clear set of guidelines governing work on those cells can be generated. I have asked Dr. Shapiro, the chairman of the National Bioethics Advisory Commission, if they would attempt to give us some preliminary information about this specific issue in the course of their larger evaluation of embryo research in general.

I hope we will have our guidelines out for public comment within a couple of months. There will be a 30-day public comment period. At that point we can begin to allow our investigators to use Federal funds.

Senator SPECTER. You say a couple of months, to April 1, and a 30-day comment period, and then that brings us to May 1?

Dr. VARMUS. Now, I do not want to prejudge exactly how my advisory committee will do its work and I do not know exactly how they will segregate the different domains of research, because they may find that some things are very cut and dried and we can move very quickly and that other issues, for example what to do in response to another set of cell lines——

Senator SPECTER. Dr. Varmus, we understand you have the problems and we are pressing on the date so we can figure out the time parameters and we know how to respond. We do not want to schedule the next hearing prematurely.

My red light is on. Let me yield to Senator Harkin.

Senator HARKIN. I just wanted to just follow up on one thing. Getting back to the time frame on how things work out, when can we expect results? For 23 years I have served on committees in the House and the Senate that deal with the National Science Foundation and now NIH. It has been my experience through those years that when you are dealing in basic research—and this is sort of basic and applied; there is kind of a fuzzy boundary here on this one—that sometimes you put a time frame, but sometimes serendipitous things happen in science. But they will not happen unless you start moving down the pathway.

So you can talk about 5 years or something, but you never know. Maybe in a year from now or something some scientist working someplace, something happens and you come up with something. That is why I think it is so important to move ahead aggressively in this because, like I say, you never know.

I just wanted to make that point, that a lot of times in science things just happen like that.

Dr. VARMUS. Well, I appreciate being castigated for my conservative position. I am usually thought of as too impetuous, so I appreciate your comments, Senator.

Senator HARKIN. Thank you, Dr. Varmus.

Senator SPECTER. We are going to ask you to stay with us, Dr. Varmus and Dr. Rabb.

I had announced at the outset that there are caucuses at 10 o'clock, at least a Republican caucus at 10 o'clock. Yours too?

Senator HARKIN. Yes.

Senator SPECTER. Also with Senator Harkin, the caucus of the Democratic Senators.

We are going to move now to panel two. We are going to conclude the hearing by 10 a.m. We have not gotten Dr. Rabb into the definitions, but we do have your very learned opinion, and if you would stand by for some dialog and questions and answers.

SUMMARY STATEMENT OF DR. ERIC MESLIN

We would like to call now Dr. Eric Meslin and Mr. Richard Doerflinger. Dr. Meslin is the executive director of the National Bioethics Advisory Commission and received his bachelor of arts degree from York University, Toronto, M.A. and Ph.D., in bioethics and philosophy at the Kennedy Institute of Ethics at Georgetown University, and author of some 35 academic articles and book chapters and peer reviewed literature.

We welcome you here, Dr. Meslin, and look forward to your testimony. As I say, the clocks are set at 5 minutes to leave maximum time for questions and answers.

Dr. MESLIN. Thank you very much, Senator, and good morning. Good morning to you, Senator Harkin.

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

Just this past week NBAC met for the 26 time since being established by President Clinton. The commission devoted the entire day, January 19, to the topic of human stem cells research, hearing testimony from a number of leading scientists, bioethicists, theologians, legal scholars, and the public. The purpose of this meeting was to provide NBAC with a deeper understanding of the ethical, scientific, legal, medical and policy issues that are raised by this important area of research.

While the commission did not reach any immediate conclusions at that meeting, nor were they expecting to, it may be helpful to describe the range of issues that were discussed and then to describe our timetable for completing this report since I understand how important it is to you.

In our view, an understanding of the legal status regarding the use of Federal funds to conduct human stem cells research provides an important context for fully understanding the ethical issues. At our recent meeting we were very interested to learn of the Office of the General Counsel's—that the Office of the General Counsel has rendered an opinion regarding whether Federal funds may be used for research conducted with human pluripotent stem cells.

We are planning to carefully review this opinion as quickly as possible since it provides one of the many pieces of valuable information we will rely on to fully address the bioethical issues involved in this area of research.

In testimony before us, Mr. Chairman, we heard some compelling arguments in favor of permitting research on human stem cells, based principally on the very promising results of previous animal studies. Several beneficial uses of these cells are anticipated and you have heard those from Dr. Varmus already.

It was also clear that a number of important scientific issues must be resolved before any actual therapies can be developed or tested in human beings. These include how to specifically direct stem cells to differentiate into specific types such as cardiac, muscle, or nerve cells, how to overcome the problem of immune rejection of such transplanted tissue, and other items.

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

Mr. Chairman, the focus of the NBAC effort is to develop sound public policy proposals based on appropriate scientific, medical, ethical, and legal considerations. In this respect, we hope to use the experiences from a number of former deliberative bodies. As with all NBAC reports, our deliberations, agendas, transcripts, and working papers will be available on our website.

In reviewing a working draft outline of the report prepared by my staff, the commission at its meeting expressed a strong interest in developing a report that was focused on a set of answerable and timely questions, but that would also be able to anticipate certain issues. The specific issues our report will address are now being developed for NBAC's consideration, but they will likely focus on some of the following points:

Is there an ethically relevant distinction between research using human stem cells derived from fetal material versus research using human stem cells obtained from existing embryos?

How should considerations about the source of human stem cells be incorporated into the analysis?

Is it ethically acceptable to produce new human embryos as a source of stem cells for research?

Finally, what is the appropriate role of the Federal Government in overseeing research of this kind?

NBAC would hope that one of the results of its deliberations on this topic would be to identify the bioethical issues that ought to be considered when supporting such research or developing guidelines for reviewing research in this area.

Now let me say a word about our timetable. As you know, Mr. Chairman, NBAC is subject to the Federal Advisory Committee Act, which you helped cosponsor. This requires that we conduct all of our business in public and come to conclusions in public. This means that any commission decisions, be they interim conclusions or final recommendations, can only occur at NBAC meetings.

We are committed to completing this report by June 1999 or thereabouts, so NBAC and its staff have mobilized to work as expeditiously as possible. Additional meetings have now been sched-

uled. In fact, we will be meeting next Tuesday and Wednesday, February 2 and 3, in Princeton, NJ, and monthly thereafter.

PREPARED STATEMENT

I should note, however, that the commission is also preparing for the possibility of being able to provide to the President conclusions on certain issues within the next few months. We are keenly aware of NIH's interest in moving forward with human stem cell research and Dr. Shapiro has already indicated to Dr. Varmus separately that if NBACreaches any interim conclusions they will be shared with NIH and others after they are transmitted to the President. Naturally, Mr. Chairman, we will be pleased to provide you and your staff with an update on our work as it proceeds.

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

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

[The statement follows:]

PREPARED STATEMENT OF ERIC M. MESLIN, PH.D.

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

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

Just this past week NBAC met for the 26th time since being established by President Clinton. The Commission devoted the entire day, January 19, to the topic of human stem cell research, hearing testimony from a number of leading scientists, bioethicists, theologians, legal scholars, and the public. The purpose of this meeting was to provide NBAC with a deeper understanding of the ethical, scientific, legal, medical, and policy issues that are raised by this important area of research. While the Commission did not reach any immediate conclusions—nor were they expecting to—it may be helpful to describe the range of issues that were discussed, and then to describe our timetable for completing this report.

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

In testimony before us, we heard some compelling arguments in favor of permitting research on human stem cells, based principally on the very promising results of previous animal studies. Several beneficial uses of these cells are anticipated, including: understanding basic and developmental biology; the development of transplantation therapies for the treatment of diseases such as Parkinson's disease and diabetes; the discovery of new drugs; and the study of infertility and birth defects.

It was also clear that a number of important scientific issues must be resolved before any actual therapies can be developed or tested in human beings. These issues include: how to specifically direct stem cells to differentiate into specific types, such as cardiac muscle or nerve cells; how to overcome the problem of immune rejection of such transplanted tissue; and how stem cells derived from fetal primordial germ cells (KG cells) differ from stem cells derived from embryonic sources (ES cells), and whether these differences have any functional importance.

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

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

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

—Is there an ethically relevant distinction between research using human stem cells derived from fetal material vs. research using human stem cells obtained from existing embryos?

—How should considerations about the source of human stem cells be incorporated into the analysis?

—Is it ethically acceptable to produce new human embryos as a source of stem cells for research?

—What is the appropriate role of the federal government in overseeing research of this kind?

NBAC would hope that one of the results of its deliberations on this topic would be to identify the bioethical issues that ought to be considered when supporting such research, or developing guidelines for reviewing research in this area.

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

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

SUMMARY STATEMENT OF RICHARD M. DOERFLINGER

Senator SPECTER. We now turn to Mr. Richard Doerflinger, associate director for policy development at the Secretariat for Pro-Life Activities, National Conference of Catholic Bishops. Welcome, Mr. Doerflinger. We appreciate your coming back, and the floor is yours.

Mr. DOERFLINGER. Thank you, Mr. Chairman.

I want to begin by noting that a point I made in my December 2d testimony on this same matter has received new support from recent events. Since then two startling scientific breakthroughs have made it even more clear that destructive embryo research is unnecessary. Advances in the use of telomerase to promote regeneration of human tissues and the new discovery that adult stem cells may be far more versatile than was once thought offer the

promise that embryonic stem cells may simply be irrelevant to future medical progress.

At the December 2d hearing Dr. Varmus noted that, while adult stem cells can be obtained from bone marrow, cord blood, and so on, they are of limited use compared to embryonic cells because they cannot form other kinds of tissues such as nerve and skin. The most recent issue of ''Science'' suggests that this judgment may well have been premature, that in fact stem cells at a later stage of development can cross over these boundaries and be adapted to perform the use of any different kind of cell.

This subcommittee has now held three hearings on one narrow avenue of research, precisely the avenue that raises the most obvious moral and legal problems, so far to the exclusion of all other alternatives, even when those avenues may be more promising. The use of adult stem cells, for example, is said to promise the complete avoidance of the tissue rejection problems that Dr. Varmus has noted still need to be solved using embryonic cells.

I would urge the subcommittee to expand its vision, to explore the alternatives that will advance medical progress and the wellbeing of patients without demeaning human dignity.

Turning now to the legal memorandum prepared by the Department of Health and Human Services, in its effort to find that Federal funding of embryonic stem cell research is consistent with Congressional intent HHS has overlooked some rather obvious facts and created its own arbitrary definition of a human embryo and, even more striking, of a human being that have no basis in biology or Federal law.

First looking at current laws on embryo and live fetal research. HHS now claims that current law on embryo research does not pose a barrier to embryonic stem cells research because the law protects only the embryo, which is an organism, and a stem cell, obtained by destroying embryos, is not an organism. HHS even cites me on this point.

But they ignore other parts of my testimony and, more importantly, ignore two important aspects of current law. First, as I noted on December 2nd, there is a factual uncertainty as to exactly what happens to the stem cells that Dr. Gearhart of Johns Hopkins University has cultured from fetal germ cells after abortions.

After being cultured, some of these stem cells have a tendency to come back together and show signs of developing as an early embryo. Whether the formation of early embryos does take place in such a culture and whether that can be prevented by adapting the research is a scientific question, cannot be answered by attorneys. A stem cell is not an organism, but the possibility must be explored that groups of stem cells may recongregate in some of this research to form an entity that is, however briefly, a living organism, in which case this research could not be funded.

HHS seeks to avoid this factual inquiry by inventing its own narrower definition of an embryo, which is not found in Federal law. Such an entity, HHS argues, cannot be an embryo because, even if implanted in a womb, it could not become a ''human being.'' Oddly enough, the key phrase ''human being'' is not defined, but from the context it seems to refer to a live-born infant. In Dr. Varmus' testimony, I noted he said a human being is a mature or-

ganism. So I am beginning to wonder whether my 6 year old son qualifies.

Embryology textbooks, however, tell us that in biological terms to embryo is a human being, and the current Federal law treats the embryo as a human subject. Since 1975, it has treated the human embryo as a human subject, to be protected from harmful research from implantation onwards, and the current embryo research rider is intended to extend that protection back before implantation, to the embryo in the laboratory.

Second, HHS seems to misread the embryo research rider itself rather obviously by saying that this research can be funded as long as Federal funds are not used for the actual destruction of the embryo. They can be used for all subsequent work with the stem cells so derived.

But Congress knows how to write a rider that says you simply cannot use Federal funds for that act. It wrote the rider that way when it dealt with creation of human embryos. It said Federal funds cannot be used for creation of embryos. Then it said Federal funds cannot be used for research in which a human embryo or embryos are destroyed or discarded or subjected to risk of harm. Obviously, that means if this is an integral part of the research protocol, even if it is not directly funded by Federal funds, the destructive harvesting of embryos is not supposed to be something that is part of a research project funded by Congress.

Finally, HHS ignores the possibility that the fetal tissue transplantation guidelines now in law apply also to the destruction of embryos in the laboratory. The statute clearly says that it covers tissue derived from embryos or fetuses, and it only allows the use of that tissue if the subject was dead before the tissue was obtained and only if the destruction was not altered in its method or timing by the needs of the research.

Well, in all of the research in which embryos are destroyed here, the destructive process is geared exactly toward obtaining usable research tissue and toward nothing else. When embryos are discarded in an IVF clinic, they do not use immunosurgery to dissect the inner cell mass from the trocoblast. They simply throw them away. Everything about the harvesting procedure is altered to obtain usable tissue, and it is the harvesting procedure that is itself the abortion or the destruction.

PREPARED STATEMENT

In conclusion, if Congress wishes to insulate its funding of medical advances from the destruction of innocent life, there is a very simple way to do just that. It should devote its funds to stem cells techniques and other promising avenues of research that in no way depend upon such destruction. In that way our government will truly serve all the people by showing that it will not promote the destruction of one human being to serve another or the development of treatments that millions of Americans would find it morally abhorrent to use.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF RICHARD M. DOERFLINGER

I am Richard M. Doerflinger, Associate Director for Policy Development at the Secretariat for Pro-Life Activities, National Conference of Catholic Bishops. I am grateful for the opportunity to present the Catholic bishops' concerns about efforts to justify the use of cells from deliberately destroyed human embryos in federally funded research.

I must begin by noting that a point I raised in my December 2 testimony before this subcommittee has received new support from recent events. I said then that the goals some wish to serve by killing human embryos for their stem cells can be achieved in other, morally acceptable ways. Even at that time, one of the advances cited by supporters as a future benefit of embryo research—the ability to grow new blood vessels in the heart—was already in clinical use in human patients with no need for embryonic cells.[1] In the six weeks that have elapsed since then, however, two startling scientific breakthroughs have made it even more clear that destructive embryo research is unnecessary. The use of telomerase to promote regeneration of human tissues,[2] and the new discovery that adult stem cells may be far more versatile than was once thought,[3] offer the promise that embryonic stem cells may simply be irrelevant to future medical progress.

At the December 2 hearing, responding to our proposed list of promising alternatives to embryonic stem cell research, National Institutes of Health director Harold Varmus said that while adult stem cells can be obtained from bone marrow, cord blood and so on, they are of limited use because they cannot form other kinds of tissue such as nerve and skin. The most recent issue of Science suggests that this judgment was premature.

This subcommittee has now held three hearings on one narrow avenue of research—precisely the avenue that creates the most obvious moral and legal problems—to the exclusion of all other alternatives, even when those avenues may be more promising. I urge the subcommittee to expand its vision, to explore the alternatives that will advance medical progress and the well-being of patients without demeaning human dignity.

I would like to turn now to the legal memorandum prepared by the General Counsel of the Department of Health and Human Services ("HHS memo"). In its effort to find that federal funding of embryonic stem cell research is consistent with congressional intent, HHS has overlooked some obvious facts, and created its own arbitrary definition of a human embryo that has no basis in biology or federal law.

Specifically, the HHS memo ignores key aspects of the current appropriations rider on embryo research (Section 511 of the Labor/HHS appropriations bill for fiscal year 1999), statutory and regulatory provisions on live fetal research (42 U.S.C. §289g; 45 CFR §46.201 ff.), and statutory law on fetal tissue transplantation research (42 U.S.C. §289g–1).

Laws on Embryo Research and Live Fetal Research

HHS claims that current law on embryo research does not cover embryonic stem cell research, because the law protects only the embryo, which is an "organism"—and a stem cell obtained by destroying an embryo is not an "organism." HHS even cites my December 2 testimony for the proposition that a stem cell is not an organism—but the authors overlook other parts of my testimony. More importantly, they ignore two important aspects of current law.

(1) Distorted definitions of "embryo" and "human being."—First, as I noted on December 2, there is some uncertainty about the status of the cells that Dr. Gearhart of Johns Hopkins University has cultured from fetal germ cells after abortions. After being cultured, some of these stem cells may have a tendency to come back together

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[1] See: "Technique grows new heart vessels," MSNBC Health, 11/9/98; "Injected Genes Help Grow Heart Bypasses," Washington Post, 11/10/98, A3.

[2] C, Morales et al., "Absence of cancer-associated changes in human fibroblasts immortalized with telomerase," 21 Nature Genetics 115–8 (January 1999); see comments in Ruth Larson, "Scientists find new life for old cells," Washington Times, 12/29/98, Al.

[3] C. Bjornson et al., "Turning Brain into Blood: A Hematopoietic Fate Adopted by Adult Neural Stem Cells in Vivo," 283 Science 534–7 (22 January 1999). See comments in: Evelyn Strauss, "Brain Stem Cells Show Their Potential," 283 Science 471 (22 January 1999); Paul Recer, "Patient's Cells May Grow New Organs," Associated Press, 1/21/99 ("If such a technique also worked in humans, embryos may not be needed for such research"); Nicholas Wade, "Cell Experiment Offers Hope for Tissue Repair," New York Times, 1/22/99, A21 (the technique avoids the "ethical considerations" arising from embryonic cells, as well as the "immune rejection problems" they can pose); Lee Bowman, "'Master cells' offer repair kits," Washington Times, 1/22/99, A9 ("it could mean that stem cells don't have to come from embryos to generate specialized cells").

and develop as an early embryo.[4] Whether the formation of early embryos takes place in such a stem cell culture, and whether it can be prevented, is a scientific question. It demands a scientific answer, before federal funds are spent on the research—because these funds by law cannot be used, even inadvertently, to create embryos which briefly develop and then die in culture. In other words, a stem cell is not an organism—but the possibility must be explored that groups of stem cells may recongregate to form an entity that is, however briefly, a living organism.

HHS seeks to avoid this factual inquiry by inventing its own definition of an "embryo"—a definition with no basis in science or law. Such an entity, HHS argues, could not be an embryo because, even if implanted in a womb, it could not become a "human being." The phrase "human being" is left undefined, but from the context it seems to refer solely to a liveborn infant.

Is "human being" intended here as a scientific term? Clearly not, since embryology textbooks tell us that in biological terms, the embryo is a human being.[5] Even the NIH's Human Embryo Research Panel, whose recommendations for federal funding of embryo experiments were found morally unacceptable by President Clinton and Congress, called the early embryo "a developing form of human life."[6]

Is it, then, a legal term? No, since the phrase "human being" is not used in this part of federal law. Instead, since 1975, federal regulations have defined the human embryo, from implantation in the womb onward, as a "human subject" to be protected from harmful experiments, regardless of whether it is expected to survive to live birth.[7] Current law on fetal research explicitly demands that a fetus to be aborted have the same protection as the fetus intended for live birth (42 U.S.C. §289g(b)).

Moreover, federal law on fetal tissue refers to the use of tissue from embryos and fetuses after a "spontaneous or induced abortion" or a stillbirth (42 U.S.C. §289g–1(g)). The HHS memo's definition would make this provision self-contradictory: A fetus that has spontaneously aborted did not have the ability to become what HHS calls a "human being," and so (by the HHS approach) cannot be called an "embryo" or "fetus" at all.

The current appropriations rider on embryo research is crystal clear. To determine whether an entity is an "embryo" we need only determine whether it is a living organism here and now (Section 511 (b)). Section 511 says nothing about restricting this term to embryos that can be shown to have the "potential to develop" to live birth. In any case, testing an embryo's ability to become a born "human being" is clearly impossible once one has used such a definition to justify destroying that embryo in the laboratory.

HHS's strange and arbitrary digression on the phrase "human being" does not serve the goal of understanding federal law, but the very different goal of justifying harmful experiments. Some researchers have actually offered to engineer lethal defects in advance into the embryos they create and destroy with federal funds—so that one could argue that these embryos would never become "human beings" and so are exempt from current law.[8]

Moreover, at this subcommittee's January 12 hearing, the theory was offered that unwanted or frozen embryos from fertility clinics can ethically be used for destruc-

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[4] In Dr. Gearhart's experiment, "embryoid bodies" had formed "complex structures" in culture "closely resembling an embryo during early development"; these structures "appear to recapitulate the normal developmental processes of early embryonic stages and promote the cell-cell interaction required for cell differentiation." M. Shamblott et al., "Derivation of pluripotent stem cells from cultured human primordial germ cells," 95 Proceedings of the National Academy of Sciences 13726–13731 (November 1998) at 13726, 13729. These remarks were cited in my December 2 testimony, at note 13.

[5] See: Keith Moore and T.V.N. Persaud, The Developing Human: Clinically Oriented Embryology (W.B. Saunders 1998)(6th edition), p. 2 ("A zygote is the beginning of a new human being"); T.W. Sadler, Langman's Medical Embryology (Williams and Wilkins 1995)(7th edition), p. 3 ("The development of a human being begins with fertilization"); William J. Larsen, Human Embryology (Churchill Livingstone 1997)(2nd edition), p. 1 ("the male and female sex cells or gametes . . . will unite at fertilization to initiate the embryonic development of a new individual").

[6] National Institutes of Health, Report of the Human Embryo Research Panel (November 1994), 2.

[7] "Human subject," in turn, is defined as a "living individual" subjected to research (45 CFR §46.102(f)); Subpart B of Part 46 provides special protections for fetuses as human subjects. "Fetus" includes "the product of conception from the time of implantation" (45 CFR §46.203(c)). Through appropriations riders, Congress since 1995 has extended this same protection to all human embryos not previously protected as human subjects.

[8] "The goal is to create a developing mass of mostly human cells that's crippled enough to prevent its development into a person, yet healthy enough during the first week of existence to produce the crucial 'stem cells' that scientists want to collect." Rick Weiss, "Can Scientists Bypass Stem Cells' Moral Minefield?", Washington Post, 12/14/98, A3.

tive research, because in any case they would not have produced a "human life." This did not refer to any defect in the embryos, but simply to the fact that parents have chosen not to let them survive. Such an approach makes a mockery of the current law, which was intended to protect such "spare" embryos from being harmed by the federal government regardless of what harm may be intended by others in the private sector. HHS would reduce current laws against harmful experiments on prenatal human life to this: Whenever someone wants to discard or destroy human embryos or fetuses instead of allowing them to survive, that very choice excludes them from the scope of the law's protection. Prenatal human beings would be protected by federal regulations only when they are in no need of such protection.

(2) Misreading the embryo research rider.—HHS's second error arises from a misreading of the appropriations rider. The HHS memo narrows its focus to the question whether a stem cell is an embryo, as though what had to be done to an embryo to obtain the stem cell is irrelevant. The implication here is that, so long as federal funds are not used for the specific act of destroying a human embryo, such funds may be used for all subsequent research on the resulting cells and tissues. But this contradicts the plain words of the appropriations rider. It does indeed ban the use of federal funds for "the creation of a human embryo or embryos for research purposes" (apparently leaving open the possibility that federal funds might be used to do life-saving or therapeutic research on an embryo that was already created without federal funds) (Sec. 511(a)(1)). But the provision goes on to say that federal funds may not be used for "research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death . . ." (Sec. 511(a)(2)). Clearly, if Congress wished to say merely that federal funds may not be used for destroying and discarding embryos, it knew how to say that; instead it used this broader phrase that is not used in the parallel clause on creating embryos.

How do we interpret the phrase "research in which?" A reasonable reading is that federal funds may not be used for research for the purpose of which human embryos were harmed or destroyed. Or, that federal funds may not be used for research that cannot be done without the prior harming or destroying of human embryos; or that such funds may not be used for research if such destruction is part of the researcher's protocol.[9] Only one interpretation is impossible, because Congress went out of its way to exclude it—the interpretation that this rider bans only the direct use of federal funds for the destructive harvesting of cells itself. That impossible interpretation is the one that HHS seems to accept.

Current Law on Fetal Tissue Research

HHS notes that "some" of the proposed research may implicate current law on fetal tissue research, citing Dr. Gearhart's experiment using fetal tissue from abortions as an example. Hinted at, but not explored by HHS, is the possibility that other proposed experiments—those relying on the destruction of human embryos in the laboratory—may also be governed by these provisions.

In fact, the law explicitly covers tissue obtained from a "human embryo or fetus" (42 USC §289g–1(g)). And since "fetus" is defined in this area of law to include any product of conception from implantation in the womb onward, the separate word "embryo" here can only refer to the unimplanted embryo—the embryo in the laboratory. In that case, the word "abortion" in this provision should be construed to include the direct destruction of an embryo in the laboratory—for otherwise the word "embryo" in the law would have no application whatever.

If this interpretation is correct—if the use of tissue harvested from embryos in the laboratory is governed by current guidelines on fetal tissue research—then such tissue cannot be used for federally funded tissue transplantation research. For such use would violate the guideline demanding that the "timing, method or procedures" for the abortion must not be altered "solely for the purposes of obtaining the tissue" for a federal research project (42 U.S.C. §289g–1(b)(2)(A)(ii)). Clearly, the destructive method used to obtain stem cells from these embryos—the use of immunosurgery to extract the inner cells—is never used to discard "spare" embryos in fertility clinics, but is employed solely to obtain usable tissue for research.[10]

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[9] By these interpretations, both Dr. West's experiment (relying on the destructive harvesting of cells from embryos created by somatic cell nuclear transfer [cloning]) and Dr. Thomson's (relying on destructive harvesting of cells from "spare" embryos from fertility clinics) are barred from receiving federal funds. A mere bookkeeping distinction between funds used to destroy the embryo and funds used to work with the resultant cells is not sufficient.

[10] Among the inadequacies in current compromise provisions on fetal tissue is the inclusion of the word "solely" here. It does not adversely affect the issue at hand, but could be used to justify federal collaboration with practitioners of the grotesque partial-birth abortion technique to obtain brain tissue for research purposes. Since the technique already involves killing a part-

To be sure, this guideline's meaning is somewhat unclear, because it refers to influencing the timing and method for "terminat[ing] the pregnancy." Ordinarily such a phrase would not be used to describe the destruction of an embryo in the laboratory. However, one must recall what Congress was trying to prevent by enacting this provision. Members had learned of a procedure in Sweden, for example, in which the unborn child intended for abortion was killed by suctioning out its brain tissue for research on Parkinson's disease, and only afterward expelled from the womb.[11] Here, the harvesting procedure was itself the "abortion," in the sense that it caused the death of the unborn child. Such abuses were to be prevented in federally funded research in the United States by this ban on altering the timing and method of abortion. The destructive harvesting of stem cells to cause an embryo's death, before it is discarded by a researcher or fertility clinic, provides a very close analogy to such abuses which Congress sought to prevent.

Indeed, this law clearly was intended to permit only the use of tissue that had been "obtained from a dead embryo or fetus"—one that died of other causes before tissue was harvested (42 USC §289g–1(g)). Even in such cases, the guidelines were intended to prevent any influence by researchers upon the decision to abort. The idea of using tissue harvested in a way that itself destroys the embryo or fetus was not proposed by any member of Congress.[12]

Conclusion

In short, there is no clear support in any relevant provision of federal law and regulations for the HHS opinion on using stem cells from deliberately destroyed human embryos—in fact, one can find much that is contrary to that opinion. The HHS memo ignores the explicit language of the current appropriations rider on embryo research; creates its own arbitrary and unsupported approach to defining a "human being"; and overlooks the possible relevance of current law on fetal tissue to the destructive harvesting of cells from human embryos.

In a broader view, it seems clear that all these laws and regulations enacted over the past 24 years were intended to ensure that the federal government never encourages the destruction of prenatal life as a source for research material. The HHS opinion would eviscerate this longstanding policy. Researchers who destroy human embryos would receive direct federal rewards for such destruction, since their lethal harvesting of tissue would make them uniquely eligible for federal grants for research on embryonic stem cells. The fact that such economic incentives would reward such destruction after the fact, instead of being bestowed in advance to pay directly for such destructive harvesting, is of no great significance.

If Congress wishes to insulate its funding of medical advances from the destruction of innocent life, there is a simple way to do just that. It should devote its funds to stem cell techniques and other promising avenues of research that in no way depend upon such killing. In that way our government will truly serve all the people, by showing that it will not promote the killing of one human being to serve another, or the development of treatments that millions of Americans would find it morally abhorrent to use.

(Attachments: Reports of recent developments in alternatives to embryonic stem cell research)

[From the Washington Post, January 21, 1999]

PATIENT'S CELLS MAY GROW NEW ORGANS

(By Paul Recer)

A patient's own cells might someday be used to grow new organs—a development suggested by a breakthrough lab experiment that found the building-block cells that normally make brain tissue in adult mice could be changed into blood-making cells.

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ly born child by suctioning out his or her brain tissue before completing delivery, it need not be altered "solely" to obtain usable tissue. Congress has repeatedly voted to make partial-birth abortion a federal crime, so presumably did not intend to state a preference for this procedure as a source of material for federally funded research.

[11] O. Lindvall et al., "Human Fetal Dopamine Neurons Grafted Into the Striatum in Two Patients With Severe Parkinson's Disease," 46 Archives of Neurology 615, 616 (June 1989).

[12] The provision's chief sponsor said: "This issue . . . is not about abortion . . . This is about what happens after an abortion takes place: Will the tissue be discarded or will the tissue be used for research . . . ?" (Rep. Waxman, Cong Record, 3/10/93, H1131; emphasis added). Harvesting of embryonic stem cells is not done after the embryo is killed; it is precisely what kills the embryo.

These so-called stem cells, the foundation source of the body's tissue, have been identified as a way to make new skin, liver and other organs. But in previous research the cells were harvested from embryos, a technique that set off a storm of ethical objections.

The new research suggests that even mature stem cells, such as from the adult brain or bone marrow, can change into the progenitor cells for other types of tissue. If such a technique also worked in humans, embryos may not be needed for such research.

"You may be able to use your own stem cells to make new tissue," said Angelo L. Vescovi, head of a team that conducted the mouse experiment. "As a concept, I don't see any problem in adult stem cells being used to make new skin, for instance."

The research shows "there are alternative strategies" to harvesting stem cells from embryos, said Dr. Ronald McKay, a National Institutes of Health researcher and a pioneer in stem cell studies.

Stem cells are the mortar and brick for growing all of the body's tissues. In a developing embryo, they produce the cells that become the body parts. After birth, some stem cells are specially programmed to replenish some tissues such as blood and skin.

Researchers earlier had isolated stem cells from human embryos or from aborted fetuses, and grew the cells in a lab. When treated with specific proteins, the cells began to grow different types of tissue cells.

That work set off a frenzy of studies. But the research was shadowed by ethical concerns because it was thought that only stem cells from embryos retained the ability to grow into a variety of organs. Many groups objected to medical experimentation with human embryos and Congress forbade federal money for such studies.

It also led President Clinton to order his National Bioethics Advisory Commission to consider the moral issues of such research. Earlier this week, NIH director Harold Varmus said his agency concluded that research with lab-grown stem cells didn't violate the congressional mandate, even though the cells originated from human embryos.

But Vescovi's work with mice suggests that any stem cell even from an adult can be reeducated to make any type of tissue.

Vescovi, of the National Neurological Institute in Milan, Italy, is senior author of a study to be published Friday in the journal Science.

"This shows that the mature stem cells are a lot more plastic than we imagined . . . they can produce a lot more cell types than was previously thought," said Christopher Bjornson, a researcher at the University of Washington, Seattle, on the team.

"A bone marrow stem cell might be able to produce tissue for the brain . . . and the skin stem cell might be able to make other cell types," Bjornson said.

In the experiment, researchers used mouse neural stem cells, which normally would develop into three types of brain and nerve tissue.

They injected the cells into the blood stream of a second group of mice whose bone marrow had been killed with radiation. The cells migrated naturally to the void left by the killed bone marrow.

Once there, they transformed from neural stem cells into blood-making cells a complete change from their original role.

But just what caused the change is unknown.

And it's unclear if adult neural stem cells have been isolated in humans, although mature stem cells for intestines, skin and blood have been identified, Vescovi said. McKay said his lab and one other had found mature human neural stem cells.

Bjornson emphasized that the new work involves only mice and that "huge steps are needed" before stem cell technology can ever be used for humans.

One key problem is learning how to direct stem cells to grow a specific organ. Although researchers at Johns Hopkins University and the University of Wisconsin, Madison, had earlier prompted stem cells to start making a variety of tissue cells, the growth was not guided toward a specific cell type.

If that problem can be solved, researchers believe it's theoretically possible that stem cells could be used to grow new livers or skin, make cells to renew a failing heart, or replace nerve cells killed by Alzheimer's.

[From the Washington Times, January 22, 1999]

"MASTER CELLS" OFFER REPAIR KITS; STUDY SUGGESTS THEY COULD BE TRANSPLANTED TO FORM TISSUE

(By Lee Bowman)

A new study suggests that adult "master cells" can be transplanted to form a number of types of tissue, a capability that could mean humans carry their own built-in tissue repair kits.

Until now, scientists have only been able to experimentally use immature stem cells cultivated from embryos and aborted fetuses for such transplants.

But if the study reported today in the journal Science can be confirmed and expanded to humans, it could mean that stem cells don't have to come from embryos to generate specialized cells. Instead, they can be moved around between different organ systems within the body.

A team led by Angelo Vescovi of NeuroSpheres Ltd. of Calgary, Alberta, and the National Neurological Institute of Italy used neural stem cells from the central nervous systems of mice in a transplant that allowed them to assume the job of bone marrow "master cells" that produce the different varieties of blood cells in a second group of mice.

"If they behave similarly to their mouse counterparts, human neural stem cells may provide a renewable source of cells that could be used in blood system reconstitution in various blood diseases and disorders," and potentially other diseases, Mr. Vescovi said.

Normally, the neural stem cells generate replacements for the major cells found in the adult brain, neurons and their support cells. Mr. Vescovi and his colleagues took some of these cells from one group of mice, genetically labeled them and injected them into the bloodstream of a second group of rodents whose bone marrow had been destroyed by a nearly fatal dose of radiation.

Once in the blood stream, the neural cells seeded the mice's bone marrow and spleen, another point for blood production, and took over the job of the destroyed blood stem cells within two weeks and produced a range of blood cells and important immune-system cells within 20 to 22 weeks.

"It took us a while to believe our own data. The tissue of the body has always been seen as unchangeable," Mr. Vescovi said.

As a comparison, researchers injected another group of irradiated mice with donated blood system stem cells from mice. They, too, took over the job of the stem cells that had been destroyed, but produced blood cells an average of three weeks faster than did the transplanted brain cells.

"This extra time required suggests that the neural stem cells undergo additional steps of fate determination, differentiation and maturation than do the blood stem cells" to take over the same job, Mr. Vescovi said.

But that they do eventually adapt themselves to work in a new system means that adult stem cells are still versatile and not genetically predestined to work only with the brain, blood, skin or intestines, for instance.

The promise of embryonic stem cells has been that they have the potential to become any type of tissue within the body as long as they are given the proper genetic signals. Scientists haven't yet figured out how to turn that switch by inserting some or all of the DNA from the cells that they want to replicate, but it had been assumed that stem cells from adults were already too set in their ways to assume new tasks.

The new study suggests that reactivating dormant genetic coding in stem cells may not require DNA transfers.

[From the Washington Times, December 29, 1998]

SCIENTISTS FIND NEW LIFE FOR OLD CELLS

REJUVENATED TISSUE COULD AID BURN VICTIMS, FEND OFF WRINKLES

(By Ruth Larson)

Aging without wrinkles? It could become a reality with a new technique for "immortalizing" human cells, Texas researchers say.

Lab cultures of human cells injected with an anti-aging enzyme have lived four times longer than their normal lifetimes. More importantly, they have shown no sign of developing cancer, as some researchers had feared.

"At long last we've learned how to put cellular aging on hold," said Jerry Shay, professor of cell biology and neuroscience at the University of Texas Southwestern Medical Center in Dallas. His research will be published today in the journal Nature Genetics.

Introducing an enzyme called "telomerase" into the cells effectively resets their biological clocks, enabling them to live and divide like young, vigorous cells.

"This doesn't mean that we're going to be able to get a whiff of telomerase and then live forever," Mr. Shay cautioned. "We're still going to die, because this won't solve all our problems. There will still be car accidents and shootings," and health problems unrelated to cellular aging.

Still, the ability to rejuvenate specific cells in the body opens up a dazzling array of possibilities. Doctors could grow skin grafts for burn victims using their own skin, insulin-producing cells for diabetics, or muscle tissue for sufferers of muscular dystrophy. And yes, they might even help combat wrinkles.

"Women—and some men—spend lots of money to get rid of wrinkles," Mr. Shay said in a telephone interview. As individuals age, their skin cells produce less of the connective tissue collagen, so the skin becomes thinner, less elastic and more susceptible to wrinkles.

"Someday it might be possible to take one of a lady's skin cells, inject it with telomerase, and rejuvenate her skin so she can make her own collagen again," he said. "It's speculative right now, but it's a very real possibility in the future."

The biotech firm Geron Corp., based in Menlo Park, Calif., has been granted the right to commercialize the technique. Geron researchers have implanted telomerase-treated human cells into mice, to see if they would form tumors in the animals. They did not.

"Even though they were immortalized, these cells behaved just like normal cells," said Calvin Harley, Geron's chief scientific officer. The cells responded to normal growth regulators that prevent runaway cell growth.

Geron is looking into several possible gene therapy applications, but Mr. Harley stressed that human applications could be years away, and only after their safety and effectiveness are proved.

Nevertheless, the Texas researchers say they have crossed a major hurdle toward such clinical applications, now that they have shown that the technique does not transform healthy cells into cancerous ones, as some critics had initially suggested.

Unlike most normal cells, which have finite lives, cancer cells can divide and reproduce indefinitely. One of the markers for cancerous activity is the enzyme telomerase.

"All cancer cells have figured out a way to become immortal," Mr. Shay explained. "Because of that, some researchers have mistakenly taken that to mean that if cells are immortalized, they will become cancerous."

Cancer, he said, is like a runaway car: "The brakes are malfunctioning, the accelerator is stuck, the steering wheel is coming off in your hands, and you have a full tank of gas."

By contrast, aging cells are like a car that has simply run out of gas. "All we've done is to put a little fuel in the gas tank; the brakes, the accelerator and the steering wheel are all still OK."

"Telomerase won't cause cancer; it won't lead to cancer," he said.

Mr. Shay's colleague, Woodring Wright, said, "The abnormalities seen in cancer cells are due to other mutations; telomerase merely allows the cells to keep dividing."

Indeed, further research might help scientists find a way to inhibit the telomerase enzyme in cancerous cells. "That could be a potent anti-cancer agent, because it would mean the cancer cells couldn't divide," Mr. Shay said.

In January, Mr. Shay and his colleagues showed that structures called "telomeres"—short pieces of DNA at the ends of chromosomes—are the biological timers that govern how many times a cell is programmed to divide in its lifetime.

Each time a cell divides, its telomeres shorten, like the fuse of a lighted firecracker. When the telomeres run out, the cell begins to die.

"It's very clear that telomeres are the key timing mechanism," Mr. Shay said.

But adding the enzyme telomerase to cells actually lengthens the telomeres, effectively giving them a new lease on life. Mr. Shay uses the term "immortal" to mean that a cell has lived at least twice its normal lifetime.

One promising application is producing healthy human cells for use in developing and testing new drugs, or screening for genetic diseases. A single, healthy human cell, dividing indefinitely, could provide an unlimited supply of cells, thereby reducing the number of animals required for lab experiments.

"This is literally changing the way we study various diseases," Mr. Shay said.

[From the New York Times, January 22, 1999]

CELL EXPERIMENT OFFERS HOPE FOR TISSUE REPAIR

(By Nicholas Wade)

In a bizarre experiment that demonstrates the surprising plasticity of the body's cells, scientists have converted mice's brain cells into blood cells.

The transformation has medical significance because if the human body's tissues should prove to be as interconvertible, patients' tissues might be repaired from their own cells.

The result in the mice was obtained with neural stem cells, which have the ability to form the three main types of cell found in the brain. Each organ of the body is thought to have its own brand of stem cells that generate all the organ's specialized cell types.

But until now, the stem cells were thought to be committed to their own organ type and unable to cross over.

A team of Italian and Canadian scientists, led by Angelo L. Vescovi of the National Neurological Institute in Milan, has now found that the neural stem cells can metamorphose into the blood-making stem cells of the bone marrow.

Dr. Vescovi's team gave mice sublethal doses of radiation to destroy their own blood-making cells, and then injected neural stem cells from other mice whose cells carried an identifying genetic tag. The neural stem cells found their way to the mice's bone marrow and started producing various types of blood cells bearing the genetic tag of the donor mouse, the scientists report in today's issue of Science.

The conversion of neural stem cells into blood cells is particularly surprising because brain and blood come from different germ layers created in the early embryo. Almost the first visible structures in animal embryos are three primary sheets of cells, known as the ectoderm, mesoderm and endoderm, from which all the tissues of the adult body develop. The brain develops from the ectoderm and blood from the mesoderm. Dr. Vescovi's work defies the widely held assumption that cells in the three lineages are permanently committed to their fate.

"It is that trinity that is now being challenged," said Ronald McKay, a brain cell expert at the National Institutes of Health. Dr. McKay said the new result showed that differentiation, the commitment of a cell to a specific fate, is not irreversible.

Dr. Vescovi said he did not know the chemical signals to which the neural stem cells were responding but assumed they were influenced by local cues in the devastated bone marrow calling for more cells.

Biologists who work with stem cells hold high hopes for using them in medicine. Stem cells, after all, are the natural source of new cells when a tissue needs to repair itself.

The human embryonic stem cells whose first isolation was reported last November have been seen as a promising source of new tissue. The embryonic stem cells can give rise to all 250 cell types of the body and in particular to the lower-level stem cells that generate each organ of the body.

But there are ethical considerations in using embryonic stem cells because the cells are derived by destroying an embryo. Also, the cells would not be immunologically compatible with a patient unless manipulated in ways that have yet to be devised.

Dr. Vescovi's work suggests that ordinary stem cells, from the skin or blood perhaps, could be acquired from the patient, thus avoiding any immune rejection problems.

"We think you can use skin stem cells to make other cells," Dr. Vescovi said. If so, skin stem cells could be harvested from a patient, and inserted into the bone marrow to make blood cells.

Dr. Vescovi believes a new branch of medicine is about to develop from stem cell biology. "The resource to heal a sick body lies in the body itself," he said.

The recent cloning of animals like mice and sheep is also an example of the new plasticity being recognized in cells. In those cases, the nucleus of a fully specialized cell was reprogrammed after being inserted into an egg cell. In Dr. Vescovi's work, the body's own local signals apparently converted the neural stem cells to a new role.

The plasticity of all these cells is possible because every cell contains a full set of the human genes or genome. Each type of cell presumably activates its own subset of genes, with all the others being switched off.

Biologists have long assumed the off-switches were put in place early in an organism's development. It now seems that the state of a stem cell's differentiation is

more of a dynamic matter, depending on whatever mix of signals it receives in its local environment.

Stem cells have become accessible to study only in the last 10 years or so. Distinguishing them from other cells required finding markers on their cell surface for which an immune-based tag could be developed. Once isolated, the cells have proved extremely unstable, either dying or developing into specialized cell types. In the body, their behavior is determined by the many cells surrounding them, a fact that must be taken into account in cultivating them.

[From CNN Interactive, November 9, 1998]

HEART RESEARCHERS REPLACE BLOCKED VESSELS BY GROWING NEW ONES

Doctors and researchers meeting at the American Heart Association's annual conference are considering an experimental treatment called angiogenesis, in which scientists use either medication or gene therapy to grow new blood vessles in the heart.

As with most experimental treatments, researchers caution that it's still too early for heart patients to get excited about the process.

But some patients already have experienced positive results.

Take real estate developer Gil Gilman.

"I could not walk across the street without suffering heart pains or angina," Gilman said. Standard drug treatments, bypass surgery and angioplasty were not successful in ending his pain.

Then doctors at Emerory University in Atlanta offered Gilman angiogenesis. Since the treatment, Gilman said, he's gotten stronger, and can "go back to doing basically anything I want to do."

Emory researchers have done safety tests of their angiogenesis procedure on 58 patients and say they are pleased with the results.

But scientists say the treatment is still in the early stages of development. One concern is that new blood vessels could grow in places where they are not wanted, like the eyes and kidneys.

Encouraging results from Tufts study

A team at Tufts University in Boston use gene therapy on 16 male patients with severe blockages. Researchers told the AHA meeting Monday the men had less chest pain after the treatment and had to take fewer drugs.

The treatment involved injecting a gene that controls production of VEGF, or vascular endothelial growth factor, which instructs the body to grow new blood vessels.

The 16 volunteers, aged 53 to 71, all had suffered heart attacks. All had blocked arteries, and all had had either bypass surgery or angioplasty to stretch open their clogged blood vessels—many of them several times.

Yet each time the blockages came back. Most of the men had such bad chest pain they could not live normal lives.

After having the VEGF injected into their hearts, all but one of the patients reported the reduction in chest pain was "marked," starting just 10 days after treatment.

Again, researchers stressed that more research is needed, but they said the potential for treatment is huge.

Dr. Jeffrey Isner said about 250,000 patients a year have ischemia, or blocked blood flow, for which bypass surgery, angioplasty or drugs have not worked.

"For these patients there is currently no other treatment option," he told a new conference.

Surgeon says valve repair can extend lives

Also at the AHA meeting Monday, University of Michigan surgeon Steven Bolling said surgical repair of a heart valve can greatly extend survival rates for patients with congestive heart failure, which claims about 250,000 lives each year in the United States.

Bolling developed the new procedure as an alternative for patients whose only other hope was a heart transplant.

CELLS ARE UNITS OF ORGANISMS—ORGANISMS ARE UNITS OF LIFE

Senator SPECTER. Thank you, Mr. Doerflinger.

Dr. Rabb, the opinion which you have rendered focuses on the proposition that, while cells are units of organisms, organisms are

units of life. Except for unicellular life, a cell does not equal an organism, which is recognized as an animal or plant, not a collection of unicells but a multicellular cooperative with the emergent properties of a whole organism.

Now, in that context how would you respond to what Mr. Doerflinger said, that stem cells may re-cogenerate into what could be a whole organism? Is that a possibility?

Dr. RABB. I cannot respond on the science, Senator Specter. The question that was asked of me was whether, if one were dealing with an entity that was not an organism, would one violate the human embryo ban, and the answer to that is no, one would not violate the ban if one were doing research with an entity that was not an organism.

If the question is whether one can do research with an organism that would otherwise be subject to the human embryo ban, the answer then again would be no, one could not do such research. But the science was not in my domain, the law was; and we did not create our own definition of an embryo. The definition we used was the one in the statute. As Senator Harkin pointed out, the statute defines ''human embryo'' in terms of an organism, and that was the question for my office. The answer we found through science was that these stem cells, not being organisms, are not subject to the ban.

Senator SPECTER. So when Mr. Doerflinger says that the destructive harvesting of embryos is indispensable, would your response be that stem cells can be obtained for this kind of research without the destructive harvesting of embryos?

Dr. RABB. That is a science question again, Senator Specter. What I can say is that, however derived not using Federal funds, once derived stem cells are not organisms and therefore are not subject to the ban.

Senator SPECTER. Well, since it is a science question, Dr. Varmus, you enter center stage here. Is it possible to have these—acquire these stem cells for the research without having the destructive harvesting of embryos?

Dr. VARMUS. At this point, Senator, no. The cells derived from embryos do require the destruction of the embryo. Obviously, in derivation from fetal tissue the tissue comes from a fetus which has already died.

Let me make a point about the issue that Mr. Doerflinger raised with respect to whether pluripotent stem cells in culture can become organisms. It is true that sometimes these cells can aggregate and may appear like one of the early phases in the development of a normal embryo. But to my mind nothing would be less ethical than to attempt to ascertain whether or not this was indeed a precursor to an organism, a viable embryo; that that would require returning that mass of cells to a uterus to ask whether it had potential to develop into a fetus and a newborn, and the prospect for developing a severely impaired individual would be enormous and to my mind a reprehensible means of doing research.

Senator SPECTER. Dr. Rabb, you made a comment that, except for the unicellular life, a cell does not equal an organism. Would you explain what you mean by the exception of the unicellular life.

Dr. RABB. I am going to try. This gets to be science again. An organism is, as it has been explained through the science, is an individual constituted to carry out all life functions. There are some unicellular animals. For those animals, the full potential of their lives inheres in a single cell. We are human beings. It is the complex interrelationship of all of the human systems that make up the organism.

Senator SPECTER. Dr. Varmus, I have one final question for you. When Mr. Doerflinger makes the point that we have ignored other new developments which might lead us to the same avenues as stem cells, are you pursuing the kinds of lines of inquiry that Mr. Doerflinger suggests at NIH?

Dr. VARMUS. Absolutely, Senator. I am glad you brought that up. Many of us were pleasantly surprised by the report that appeared in "Science" this week, a copy of which I have given to your staff, that shows that stem cells taken from the mouse brain and grown in culture can be returned to a mouse and produce blood cells.

This indicates a level of plasticity that was unexpected and of course a very promising area of research. But I must emphasize, this is one report carried out in one way with one strain of mice. Whether this formulation or this approach will be applicable in other strains of mice, other animals, with other types of cells, whether we can identify what is responsible for reprogramming the cell, all matters of conjecture.

My view is, yes, we should be pursuing this and many other lines of investigation with relation to many kinds of stem cells. But to say that we should put our eggs in one basket and not in all the available baskets would be a serious mistake.

Senator SPECTER. So you are saying that NIH has eggs in those other baskets?

Dr. VARMUS. Absolutely.

Senator SPECTER. Senator Harkin.

Senator HARKIN. Thank you, Mr. Chairman.

Mr. Doerflinger, I was just reading an article you had written here for the "National Right to Life News" which I found interesting. Let me just ask you, in vitro fertilization is not illegal, is it?

Mr. DOERFLINGER. No.

Senator HARKIN. Is it immoral?

Mr. DOERFLINGER. In Catholic teaching there are moral problems with it, yes. There is a good bit of research, however, involving in vitro fertilized embryos that is illegal in various States.

Senator HARKIN. I do not think the church has taken a position that an infertile couple cannot engage in in vitro fertilization. I do not—maybe I am wrong.

Mr. DOERFLINGER. Catholic teaching does not accept in vitro fertilization as a solution for infertile couples. It urges them to pursue fertility treatments that will help their sexual union to be procreative if that is what they want, rather than to substitute a laboratory procedure for that.

Senator HARKIN. Well, I will have to check, but I did not think that they had taken an absolute position against in vitro fertilization. So I have in vitro fertilization——

Mr. DOERFLINGER. I am pretty close to that situation, Senator.

Senator HARKIN. Huh?

Mr. DOERFLINGER. Working for the National Conference of Catholic Bishops, I am fairly close to that situation.

Senator HARKIN. Well, I am sure you would be. I would hope so. But I still, I did not think that they had taken a position that said that you cannot use in vitro fertilization. Maybe I am wrong. I do not know.

Mr. DOERFLINGER. I will be glad to send you the document on it.

Senator HARKIN. Am I wrong? Have they taken an absolute position on it?

Mr. DOERFLINGER. I never like to say that up front to a Senator, but I think so, Senator. I will send you the documents on it.

Senator HARKIN. Well, I do not know. I mean, you are the authority on that. I do not know. Send it to me.

Mr. DOERFLINGER. Among the concerns that have been raised beyond the Catholic Church about the procedure is the prospect for abuses to the embryos that come out of the procedure, the culling of high quality embryos, the discarding of embryos, the selective reductions that are proposed when too many of the embryos implant. These are all part of the——

Senator HARKIN. So we have got in vitro fertilization. At least it is not illegal. We have a lot of it going on, and obviously there are a lot of leftovers that are frozen. What happens to them?

Mr. DOERFLINGER. Some are frozen indefinitely. Some are ultimately used for later attempts at having a child, and some are experimented upon and some are thrown away.

Senator HARKIN. Some are destroyed. Well, if in fact this is not illegal and they are in fact, some are destroyed, why not use them to get the pluripotent cells that we need to do the kind of research that may help us in the future alleviate human suffering? I do not understand why we cannot do that.

Mr. DOERFLINGER. Well, Senator, I think that is the question that we explored a little bit at the last hearing. There are lots of things that go on in the private sector that are going to go on anyway that Congress has decided not to add its encouragement to by giving Federal funds, abortion being an excellent example. It is not only legal—I mean, it is more legal than destructive embryo research, which is a felony in several States. It is defined as a constitutional right. But Congress has decided we are not going to use Federal funds to give our endorsement to it.

I think you could just as well say, if you are walking down the street and you find a bunch of big tough guys beating up an old man, the question arises whether before they are done with him you could take his liver because you need it, thus killing him a little earlier. I do not think whatever somebody else is doing out there in the private sector that they are going to do anyway has much influence on what Congress has to decide in its policy decision on what to promote.

See, in this case, this is not a case analogous to the fetal tissue situation where the abortion has been done and, as Henry Waxman said in 1993 in the House floor, the only question left is whether to throw away the tissue that is left after the fetus is dead or make use of it. Here is a case where the researchers' harvesting proce-

dure does the destruction itself. That is a very different moral proposition.

Senator HARKIN. But it is going to take place, as I said, anyhow.

Mr. DOERFLINGER. It is going to take place anyway. Senator, you and every other Senator in the Senate voted in 1997 to reject Federal funding of euthanasia, even though all of those people are going to die pretty soon anyway. But it makes a difference whether they are going to die of some other cause or whether the government is going to help kill them.

Senator HARKIN. Well, as you said here in this article, you said that such experiments that we are talking about here create new human life. I thought we got through that. Organisms, these are not organisms. They cannot develop into full human life. Every scientist I have ever asked that question to says that. Yet you seem to want to bring it back across that boundary line again, and I just do not understand that.

Mr. DOERFLINGER. I think what I was saying, Senator, was there is a factual uncertainty about one of these experiments, Dr. Gearhart's, which can be settled in a factual way. It is an uncertainty he himself has. The answer that Dr. Varmus has given is intriguing, because if we really do not know and there is no ethical way to find out, that might answer the question in the direction of saying we cannot fund it then.

But my broader question was simply that HHS gave an answer to that question which is probably right as far as it goes, but it is the wrong question, because the embryo research rider was not intended only to say that you cannot use Federal funds for the destructive act itself. It was designed to prevent Federal funding of an entire research project in which these are destroyed, even if they are destroyed with private funds.

Senator HARKIN. Well, I disagree with that interpretation. I adamantly disagree. That may be your interpretation. I do not believe Congress—you would have to show me report language or anything else that indicates that we intended it to be that broad and that encompassing. I do not believe that.

Mr. DOERFLINGER. You have two clauses there right next to each other. The first one says you cannot use Federal funds for creation of embryos. If your interpretation is right, I cannot think of a blessed reason why they did not just say Federal funds cannot be used for destroying embryos. They did not say that. Instead they said—they used an entirely different phrase right next to the first one saying, cannot be used for research in which embryos are destroyed or discarded.

Now, that cannot mean the same thing as the first clause because it is very deliberately written more broadly.

Senator HARKIN. I have to think. You lost me on that one.

Mr. DOERFLINGER. If you want to rewrite the rider, then we can have a debate about that.

Senator HARKIN. This is it right here. "None of the funds made available by Public Law 104–91 may be used for: [1] the creation of a human embryo or embryos for research purposes or [2] research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risks of injury or death greater

than that allowed for research on fetuses in utero under 45 CFR,'' etcetera.

''For the purposes of this section,'' I will read one more time, ''the phrase' human embryo or embryos' shall include any organism not protected as a human subject under 45 CFR 46 as of enactment of this act,'' etcetera, etcetera, etcetera.

Now again, I think that is the essence of the finding at HHS. It is clear that these are not organisms——

Mr. DOERFLINGER. That the stem cells are not organisms.

Senator HARKIN (continuing). and as such cannot be covered by that law, Mr. Doerflinger. Now, if you want to change the law——

Mr. DOERFLINGER. I am not talking about the stem cell being an embryo. I am talking about the stem cell that you have to kill to get the stem cells——

Senator HARKIN. Wait a minute.

Mr. DOERFLINGER [continuing]. as an integral part of that research protocol.

Senator HARKIN. You are saying stem cell you have to kill to get the stem cells. I do not understand that, what you just said. You said the stem cell you have to kill to get the stem cell.

Mr. DOERFLINGER. No, I said the embryo you have to kill to get the stem cells. The stem cells are simply the inner cell mass of an embryo. The way the stem cells is obtained is by doing microsurgery on an embryo and sucking out the inner cell mass to provide stem cells for culture.

What I am saying is the destruction of that initial embryo in two of the three experiments we are talking about, because Dr. Gearhart's experiment is using fetal tissue, but in Dr. West's and Dr. Thomson's experiments an integral part of the research protocol is you must arrange for these embryos to be destroyed by the harvesting of these cells. It is not after the embryo is dead. It is what kills the embryo. It seems to me that that is what Congress was intending to prevent.

Senator SPECTER. Senator Harkin, do you have further questions?

Senator HARKIN. No, thank you very much, Mr. Chairman.

Thank you, Mr. Doerflinger.

Senator SPECTER. Thank you.

Senator Hollings.

Senator HOLLINGS. Would you care to comment, Dr. Varmus.

Dr. VARMUS. I think the point is the law to our minds reads quite clearly, and it is not our job to try to discern intent when intent is not described by report language or other means of discernment. So our view is that there is a very clear distinction to be made between research in which stem cells that have been developed in one laboratory by one procedure are then used by other investigators to support other kinds of research that is not research in which an embryo, an organism, is subjected to risks greater than those that are dictated by other statutes.

Senator HOLLINGS. Thank you, Mr. Chairman.

Senator SPECTER. Thank you, Senator Hollings.

We are now slightly past 10 o'clock, so we are going to have to adjourn. We thank you very much for coming again today, and this is obviously going to be an ongoing matter of great public interest

as we pursue the steps which are set up. We appreciate your participation, Mr. Doerflinger, to give us your analysis. You have immunity here when you criticize Senators. You can say Senators are wrong. That comes under——

Senator HOLLINGS. We hear that every day.

CONCLUSION OF HEARINGS

Senator SPECTER. Senator Hollings is accurate about that. But you have a privilege to make those statements. We are here to have an exchange, and we appreciate your incisiveness and your study and your knowledge of the field.

We thank you, Dr. Varmus, Dr. Rabb, and Dr. Meslin, and stay tuned. Thank you all very much for being here, that concludes our hearing. The subcommittee will stand in recess subject to the call of the Chair.]

[Whereupon, at 10:02 a.m., Tuesday, January 26, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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