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ADULT STEM CELL RESEARCH: SUCCESSES FROM THE FIELD

HEARING

BEFORE THE

SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE

OF THE

COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION
UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

JULY 14, 2004

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SENATE COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

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ADULT STEM CELL RESEARCH: SUCCESSES FROM THE FIELD

WEDNESDAY, JULY 14, 2004

U.S. SENATE,
SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE,
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION,
Washington, DC.

The Subcommittee met, pursuant to notice, at 2:35 p.m. in room SR–253, Russell Senate Office Building, Hon. Sam Brownback, Chairman of the Subcommittee, presiding.

OPENING STATEMENT OF HON. SAM BROWNBACK, U.S. SENATOR FROM KANSAS

Senator BROWNBACK. This hearing will come to order. Thank you all for joining us today in an exciting hearing.

Today's hearing is about miracles and answered prayers. People have prayed for cures to lives destroyed by accidents and ravaged by diseases. You'll see, on video, paraplegics walk—with aid, but walking, nonetheless. You will see Parkinson's dealt with—still with difficulty, but being dealt with. Today's hearing's about miracles, prayers answered, prayers yet to be answered, because we have much yet to do.

I'm delighted to be joined by my colleagues on this discussion about adult stem cell research. That's what the hearing will be about, that's what it will focus on. This is a noncontroversial area in stem cells. We've all heard a lot about stem cells. The adult stem cell area, umbilical cord-blood stem cells are ones that nobody disagrees with, that everybody is supportive of. Everybody is supportive of the scientific research, and the things that are taking place are absolutely profound—I would put in the category of miraculous and answers to prayer. And you will see some of that on display today.

But there is much to be done. I think we need to continue the funding aggressively in the field adult stem cell research, in pushing that forward so that we can find more cures for more types of diseases that ravage the body and that hurt us all.

We will not be dealing with the issue of embryonic stem cells today in the hearing. The hearing's focused on adult stem cells. That's what we've intended to put forward and to try to address at this hearing. There is a controversial area on stem cells, in the embryonic field. That has been the subject of a number of different hearings, particularly in the Appropriations Committee, and we'll not be addressing that issue today.

My hope is that at this hearing we will be able to engage people in a dialog of hope; and be able to show people with devastating diseases or injuries promise and hope to move forward in life. We'll have a panel of experts and a panel of patients—experts to tell us what is taking place in the field; the patients to show us what's taking place in their lives.

And I look forward to having this good news hearing. There are always many controversial subjects; we face many difficult subjects. This is a good news hearing. We've got much yet to do, but there is some good news to be celebrated here today.

With that, I look forward to the presentations, and I want to turn to the Ranking Member, Senator Wyden, for his opening statement.

STATEMENT OF HON. RON WYDEN,
U.S. SENATOR FROM OREGON

Senator WYDEN. Thank you very much, Mr. Chairman. And, as always, you know how much I enjoy working with you. And having chaired this Subcommittee in the past, I'm acutely aware that this issue generates such passions that it is almost physiologically impossible to be unaware of the politics of stem cell research. No Senator who participates in a hearing on this subject could possibly feel that they're being recast in an updated version of the movie Casablanca, and then pipe up that they're just shocked and absolutely amazed about the presence of politics.

Now, that having been said, I'm hopeful—as I think your opening statement indicated, Mr. Chairman—I'm hopeful that this hearing can help inject, if ever so slightly, a bit more nonpartisanship with respect to this issue. And I come to this issue in a nonpartisan way with the view that I think while the research shows that using adult stem cells can help some people, there are millions of Americans who suffer from a host of devastating diseases, and their valiantly supportive families, who I believe deserve more.

And my concerns with respect to this issue and the science, Mr. Chairman, can be summed up in just one paragraph that I pulled off the NIH website a few minutes ago. On the NIH website, there's a section called "Facts on Stem Cells." And I would just like to read into the record one paragraph with respect to what is on the government's official website with respect to how adult stem cells are used and the opportunities that they present to the American people.

I quote here, "There are currently several limitations to using adult stem cells. Although many different kinds of multipotent stem cells have been identified, adult stem cells that could give rise to all cell and tissue types have not yet been found. Adult stem cells are often present in only minute quantities, and they can, therefore, be difficult to isolate and purify. There is also evidence that they may not have the same capacity to multiple as embryonic stem cells do. Finally, adult stem cells may contain more DNA abnormalities caused by sunlight, toxins, and errors in making more DNA copies during the course of a lifetime. These potential weaknesses might limit the usefulness of adult stem cells."

Mr. Chairman, I would just ask that the "Facts on Stem Cells," the portion of which I've written, could be entered into the record at this point.

Senator BROWNBACK. Without objection.

[The information referred to follows:]

An excerpt from the NIH website (*http://stemcells.nih.gov/info/faqs.asp*)

There are currently several limitations to using adult stem cells. Although many different kinds of multipotent stem cells have been identified, adult stem cells that could give rise to all cell and tissue types have not yet been found. Adult stem cells are often present in only minute quantities and can therefore be difficult to isolate and purify. There is also evidence that they may not have the same capacity to multiply as embryonic stem cells do. Finally, adult stem cells may contain more DNA abnormalities—caused by sunlight, toxins, and errors in making more DNA copies during the course of a lifetime. These potential weaknesses might limit the usefulness of adult stem cells.

Senator WYDEN. Mr. Chairman, let me just close by way of saying I think we are going to have a chance to explore this issue in some detail. There are a lot of ramifications to it. I'm interested in talking to the scientists, for example, with respect to how this is going to affect private-sector research. Given the government's limitations on funding this research, I think it's going to have debilitating effects, in terms of generating the dollars that are going to be needed for private-sector research into other areas. But, more than anything, I come today—and you and I have worked together on so many areas—I come to say that I'm very much aware of the passions on this issue, and—all sides—and I am hopeful that we can use this hearing to try to find a bit more common ground, because that's what the American people, I think, are calling for in this area, so that we can find the cures and therapies that you correctly stated in your opening statement would give families hope. And I look forward to working with you on this.

Senator BROWNBACK. Thank you, Senator Wyden.

Senator Lautenberg?

STATEMENT OF HON. FRANK R. LAUTENBERG, U.S. SENATOR FROM NEW JERSEY

Senator LAUTENBERG. Thanks, Mr. Chairman.

I think it's fair to say that we'll all agree that stem cell research is critical to our mission to fight and cure disease in this country and throughout the world. Unfortunately, this research continues to become embroiled in a political controversy. And I listened very carefully to the Chairman's delineation of the ground that we're going to cover, and I think it's, sort of, akin to a discussion on research on cancer that we say, "Well, we can only look at one type of treatment. We can only look at radiation. We can only look at diet, or we can only look at chemotherapy or something." And if you want to cure cancer, I don't think you can put out some of those methods that work. Some need one another to work well. And the debate over whether we should pursue adult stem cell research or embryonic stem cell research sets up an unreasonable choice.

Both types of stem cell research should be pursued simultaneously. Each offers the potential for cures. Neither is a substitute for the other. No promising stem cell research should be stopped. Stem cell research, particularly the burgeoning field of embryonic

stem cell research, has tremendous potential to help us better understand, treat, and even cure deadly and disabling diseases like diabetes and cancer, Parkinson's, Alzheimer's, and Multiple Sclerosis. Stem cell research could help us cut the incidence of heart disease, the Nation's leading killer.

Most Americans support stem cell research, as do Members of Congress from both sides of the political aisle. And former First Lady Nancy Reagan, who spent 10 years watching her husband suffer from Alzheimer's, is a stringent advocate. Virtually every major medical, scientific, and patient advocacy groups support embryonic cell research. And I'm talking about the American Medical Association, the Federation of American Societies for Experimental Biology, the Juvenile Diabetes Research Foundation, the Parkinson's Action Network.

In my view, President Bush's stem cell research policy does sacrifice some sound science, and I wish it weren't so. President Bush's stem cell research policy is, in effect, denying millions of people suffering from physically and mentally debilitating diseases, illnesses, and injuries from being cured.

And I know that the views of those—and I have great respect for the Chairman—of those who oppose embryonic stem cell research are sincere. But I've met with too many diabetic children and their families. I've see how much they suffer, and I simply can't tell these children or their parents that, in the hierarchy of rights, a week-old undifferentiated cell is more important than they are and cannot be used in researching, treating, or possibly curing their terrible disease.

The millions of men, women, and children who are suffering from diabetes and other life threatening diseases, illnesses, and injuries are engaged in a race against time. Talk to these children, and understand how uncomfortable life is, even as they live it precariously. And it's our responsibility to make sure that they benefit as quickly as possible from the wonders that modern science, medicine, and technology have to offer.

Now, Mr. Chairman, one of the things that I am very proud of in my lifetime is a facility called the Lautenberg Cancer Research Center, named for my father, who died when he was 43 years old, and was a health faddist, as in those days. But when cancer overtook, there was no way to overcome.

And one of our outstanding witnesses here, Dr. Weissman, is going to be testifying, and he's just come back from a one week lecture at the Lautenberg Cancer Research Institute, which is in Jerusalem, where a friend of mine moved many years ago and asked if I would help in establishing a Lautenberg Cancer Research Center, and I, fortunately, was able to provide the funding for it, and I look forward to his testimony. And I review the work that we do at the Lautenberg Cancer Research Center, and stem cells are an important part of the agenda. And I hope that we'll be able to move the debate along so that we don't engage in a political difference and permit science to run its own course.

Thank you.

Senator BROWNBACK. Senator Nelson?

STATEMENT OF HON. BILL NELSON, U.S. SENATOR FROM FLORIDA

Senator NELSON. Mr. Chairman, ever since I had the privilege of conducting the experiment proposed by the Comprehensive Cancer Center at the University of Alabama at Birmingham onboard the 24th flight of the Space Shuttle, and where I had one little opportunity to glimpse into the work of scientists, my admiration and appreciation and conclusion is, let's don't hold them back.

Clearly, when we get into the question of life, it's going to be an emotional consideration. But here, we're talking about research on stem cells that are not as a result of a fertilized egg, but, rather, stem cells that have been artificially created, implanted, and produced. For us to get this into the realm of saying we're going to stop this, with all of its potential of saving life, seems to me not to be the place to draw the line.

So I'm looking forward to the testimony today. Thank you, Mr. Chairman.

Senator BROWNBACK. Thank you very much.

Gentlemen, we'll call up the first panel. And if you could come up, we would appreciate that.

It will be a panel of experts, Dr. Michel Levesque, of Beverly Hills, California; Dr. Jean Peduzzi-Nelson, of University of Alabama at Birmingham; and Dr. Irv Weissman, of Stanford University Medical School, in California.

I want to thank the panel for coming forward, and I thank you in advance for your testimony.

I would note that your entire written statement will be put in the record at the outset, and so you're welcome to just summarize, if you would like to, or you can present your statements, as well. I would appreciate it if you could keep them as concise as possible so we could have plenty of time for exchange and interchange.

Dr. Levesque, we appreciate your testimony.

STATEMENT OF MICHEL F. LEVESQUE, M.D, FRCS(C), FACS, CEDARS-SINAI MEDICAL CENTER, LOS ANGELES, CALIFORNIA; ASSOCIATE CLINICAL PROFESSOR, UCLA SCHOOL OF MEDICINE AND MEMBER OF UCLA BRAIN INSTITUTE; CHAIRMAN, FOUNDATION FOR NEURAL REPAIR

Dr. LEVESQUE. Thank you, Senator. Good afternoon.

Senator BROWNBACK. Move your—you're confusing us here, your signs are off a person. So, Dr. Weissman, if you'd pull yours in——

[Laughter.]

Senator BROWNBACK. Thank you.

Dr. LEVESQUE. So, good afternoon. My name is Michel Levesque, and I'm a physician, scientist, and neurosurgeon based at Cedars-Sinai Medical Center in Los Angeles. I'm also an Associate Clinical Professor of Neurosurgery at the UCLA School of Medicine, and member of the UCLA Brain Research Institute. I'm also the founder of NeuroGeneration, a biotech company pioneering neural stem cell therapies, and Chairman of the Foundation for Neural Repair, a not-for-profit foundation sponsoring free clinical research to accelerate human trials using neural stem cells.

Mr. Chairman and Members of the Subcommittee, I want to thank you for the opportunity to testify today on our current expe-

rience with the use of stem cells in humans, and, more specifically, adult neural stem cells for neurological disorders like Parkinson's disease.

Although nonpartisan, my testimony attempts to provide a realistic perspective on the promises and limitations of cell therapy for neurological disorders, either from embryonic or adult-derived stem cells.

As a scientist and physician treating patients with irreversible neurological disorders, it is of utmost importance to understand both the fact and the fiction of cell therapy, and the hopes it generates in our patients and their families.

What is stem cell therapy? Stem cell research and therapy are some of new several tools, like vaccines, genes, or small molecules, targeting diseases not treated by traditional medication therapies.

Stem cell research looks at basic mechanism of cell cycle at sequential expression of different genes during the formation of the embryo and cellular specialization and differentiation into different tissues. Stem cell research also explore the causes of disease, the mechanisms of cell degeneration and cell death.

Stem cell therapy attempts to replace the cell loss and induce repair mechanism in models of disease. Clinical research and therapeutic trials, on the other hand, study the safety and efficacy of stem cells in patient with certain disorders.

Neural repair and neural transplantation using cell therapy aim at introducing cellular products to replace the deficient cells, or induce local neural repair in the central nervous system.

What are human adult neural stem cells? Since 1996, our laboratories have been involved with the isolation of human adult-derived neural stem cells obtained from patients undergoing neurosurgical procedures. In the adult brain, these cells cannot, on their own, trigger repair responses. However, if placed in experimental conditions, stimulating certain genes, these neural stem cells can be awakened and begin to divide and regenerate along similar steps of normal development.

These newly created neural stem cells can grow for several months in laboratory conditions, reaching several millions in number. The ability to self-replicate and form all types of cells found in the central nervous system can be verified in vitro under controlled conditions.

Prior to transplantation, neural stem cells are then differentiated, stopping the replication process to produce mature neuron of different types, including dopamine-secreting neurons, which are deficient in Parkinson's disease.

These newly formed cells are unadulterated, having not been exposed to years of chronic oxidative stress or other predisposing environmental factors leading to cell damage and cell death.

Adult neural stem cells represent a new source of cell replacement with identical genetic material to the patient, and mitigate the risk of immune rejections and transmittable disease.

Can stem cell therapy help neurodegenerative disorders such as Parkinson's disease? Parkinson's disease is associated with a progressive cell loss of midbrain dopamine-secreting neurons. The causes of Parkinson's disease remain unknown. Like Alzheimer's disease, there is evidence showing that a combination of environ-

mental factors and genetic predisposition are precursors of the disease. Current animal models derived from toxic exposure or transgenic manipulations do not replicate all changes found in human brain.

In fact, Parkinson's disease is much more complex in human patients because of secondary chemical changes throughout the rest of the brain superimposed on long-term medical therapy.

Embryonic stem cells have the potential, virtual potential, to generate any type of cell in the body. One of the key problem, however, is to elucidate the proper steps along the formation of neural stem cells, and then to achieve proper differentiation.

In addition, there remain risks of unstable phenotypic expression, possible transdifferentiation into other types of tissue causing tumors, immune reactions in the host brain, and questionable functional benefits.

Currently available embryonic cell lines are not appropriate to answer these scientific questions. Embryonic cell has yet to be scientifically proven as safe and even effective in human patients. On the other hand, mature neurons derived from the patient's own brain can be transplanted back safely and improve symptoms.

We recently presented a clinical outcome of this autologous method at the meeting of the International Congress of Parkinson's Disease in Rome. We previously transplanted the patient with advanced Parkinson's disease with differentiated neurons derived from an initial biopsy. At 3 years post-operatively, the UPDRS score improved by 81 percent while on medication, and 83 percent while off medication. We demonstrate here the long-term clinical improvement of Parkinson's disease symptoms in a single patient.

To conclude this presentation, adult human neural stem cells derived from a patient's own tissue can become a source of replacing neurons useful for grafting in the treatment of neural degenerative disorder.

Degenerative and traumatic disorders of the brain represent an enormous challenge to the patient, their family, and healthcare provider. The ethical debate between the embryonic stem cell proponents and those who are opponents, opposed to their use, distracts from other avenues with promising outcomes. It also overlooks other ethical issues of resource allocation between basic research, clinical research, patient care, and health insurance.

Scientific knowledge has rapidly progressed in the last 5 years, and stem cell research remains a very promising field for neurological disorders. The ethical debate we are facing today is to access proper funding to proceed with human clinical trials using neural stem cells. Our challenge is to build the proper infrastructures committed to these long-term goals. For a fraction of the price of a B–1 bomber, millions of lives can be improved, if not saved, with the use of these neural stem cells.

Thank you.

[The prepared statement of Dr. Levesque follows:]

PREPARED STATEMENT OF MICHEL F. LEVESQUE, M.D., FRCS(C), FACS, CEDARS-SINAI MEDICAL CENTER, LOS ANGELES, CALIFORNIA; ASSOCIATE CLINICAL PROFESSOR, UCLA SCHOOL OF MEDICINE AND MEMBER OF UCLA BRAIN INSTITUTE; CHAIRMAN, FOUNDATION FOR NEURAL REPAIR

My name is Michel Lévesque, and I am a physician, neuroscientist and neurosurgeon based at Cedars-Sinai Medical Center in Los Angeles. I am Associate Clinical Professor of Neurosurgery at the UCLA School of Medicine and member of the UCLA Brain Research Institute. I am also the founder of *NeuroGeneration,* a biotechnology company pioneering autologous neural stem cell therapies, and Chairman of the Foundation for Neural Repair, a not-for-profit foundation, sponsoring translational research to accelerate human trials using neural stem cells.

Mr. Chairman and members of the Subcommittee, I want to thank you for the opportunity to testify today on our current experience with the use of stem cells in humans, and more specifically, adult neural stem cell-derived neurons, for neurodegenerative disorders like Parkinson's disease.

Although non-partisan, my testimony attempts to provide a realistic perspective on the promises and limitations of cell therapy for neurological disorders, either from embryonic-or adult-derived stem cells.

As a scientist and physician treating patients with irreversible neurological disorders, it is of utmost importance to understand both the fact and fiction of cell therapy and the hopes it generates in our patients and their families.

What Is Stem Cell Therapy?

Stem cell *research* and *therapy* are some of several new tools, like vaccines, genes or small molecules, targeting diseases not treated by traditional medication therapies.

Stem cell *research* looks at basic mechanisms of the cell cycle, at sequential expression of different genes during the formation of the embryo, and at cellular specialization and differentiation into different tissues. Stem cell research can also explore the causes of diseases, cell degeneration and cell death.

Stem cell *therapy* attempts to replace the cell loss and induce repair mechanisms in models of disease. *Clinical research* and therapeutic trials, on the other hand, study the safety and efficacy of stem cell therapy in patients with certain disorders.

Neural repair and neural transplantation using cell therapy aim at introducing cellular products, or biological modifiers, to replace the deficient cells and/or induce local neural repair in the central nervous system.

What Are Human Adult Neural Stem Cells?

In nature, neural stem cells are formed after a cascade of sequential events activates genes within embryonic cells during development. They are derived from a specific layer of the embryo and can only become, under normal conditions, precursors of cells found only in the central nervous system.

Since 1996, our laboratories have been involved with the isolation and characterization of human adult-derived neural stem cells, obtained from patients undergoing neurosurgical procedures. In the adult brain, these cells cannot on their own trigger repair responses. However, if placed in experimental laboratory conditions stimulating certain genes, these neural stem cells can be "awakened" and begin to divide and replicate events of normal development.

These newly created neural stem cells can grow for several months in laboratory conditions reaching several millions in number, a process called cell expansion. Their ability to self-replicate and form all types of cells found in the central nervous system can be verified *in vitro* under controlled conditions. They can be placed in storage or maintained in sterile incubators until ready for use.

Prior to transplantation, neural stem cells are then exposed to a modified environment triggering differentiation, stopping the replication process to produce mature neurons of different types, including dopamine-secreting neurons, which are deficient in Parkinson's disease. In the laboratory, differentiated neurons can be characterized with specific markers, and their function demonstrated by the increased production of dopamine.

These cells have survived transplantation and corrected motor deficits in a rat model of Parkinson's disease. Our animal studies showed that human adult neural stem cells do not divide once differentiated, do not form aberrant tissue or tumors after chronic transplantation, and have normal karyotypes (number of chromosomes). Sterility is documented throughout the expansion phases.

These newly formed cells are unadulterated, having not been exposed to years of chronic oxidative stress and other predisposing factors leading to neurodegeneration. Autologous adult neural stem cells represent a new source of cell replacement with identical genetic material to the patient, and mitigate the risks of immune rejections

and transmittable diseases generally associated with tissue transplants from a source external to the patient such as HIV, Encephalitis, Hepatitis and Creutzfeld-Jacobs Disease.

Can Stem Cell Therapy Help Neurodegenerative Diseases Such as Parkinson's Disease?

Parkinson's disease is associated with a progressive cell loss of midbrain dopamine-secreting neurons. Dopamine is an essential brain chemical for proper modulation and execution of motor function. Because of the limited spatial involvement and biochemical specificity, this disease may seem relatively easy to repair. Dopamine neurons delivered by fetal transplantation previously were shown to help certain patients with Parkinson's disease, but had significant risk factors, complications, and ethical issues.

The causes of Parkinson's disease remain unknown. Like Alzheimer's disease, there is evidence showing that a combination of environmental factors and genetic predisposition are precursors to the disease. Current animal models, derived from toxic exposure or transgenic manipulation, do no replicate all changes found in the human brain.

In fact, Parkinson's disease is much more complex in human patients because of secondary physiological and chemical changes throughout the rest of the brain, superimposed on long-term medical therapy. Indeed one of the major complications of dopamine drug therapy is the paradoxical creation of dyskinesia, another movement disorder involving uncontrollable thrashing movements.

This complication was also found in some patients receiving fetal transplantation, suggesting that an uncontrolled delivery of excessive dopamine may not be beneficial. Stem cell-derived products have the advantages of being produced under controlled environment and characterized both in their types and function prior to transplantation.

Embryonic stem cells have the potential to generate any type of cells and presumably can be guided in their differentiation to generate an unlimited number of dopamine neurons. One of the problems is to understand the proper steps to guide the gene expression along the formation of neural stem cells and then to achieve proper differentiation.

In addition there remain risks of unstable phenotypic expression, possible transdifferentiation into other types of tissue causing tumors, immune reactions in the host brain and questionable functional benefits. Several additional studies are needed in order to answer these questions and objectively compare these "off the shelf" cell lines to our customized approach using autologous adult neural stem cells.

While the use of somatic nuclear cell transfer (SNCT) technology could decrease risks of immune reactions, this area of research minimizes the importance of "imprinting", or influences of the extra-nuclear material on normal cellular development.

Currently available embryonic cell lines are not appropriate to answer these scientific questions. Embryonic cell therapy has yet to be scientifically proven as safe, if even effective, in human patients.

Mature Neurons Derived from the Patient's Own Brain Can Be Transplanted Back Safely and Improve Symptoms

We recently presented the clinical outcome of our autologous method at the International Congress of Parkinson's disease and Movement Disorders in Rome. In accordance with our institutional review board, we transplanted a patient with advanced Parkinson's disease with differentiated neurons derived from an initial needle biopsy. At three years post-operatively, the overall Unified Parkinson's Disease Rating Scale (UPDRS) improved by 81 percent while "on" medication and 83 percent while "off" medication. We demonstrated here the long-term clinical remission of Parkinson's disease symptoms in a single patient.

Because of their biocompatibility, safety and potential integration into the host striatum, autologous adult neural stem cells and stem cell-derived neurons represent an effective alternative to current cell therapy aimed at the restoration of dopamine neuronal loss in Parkinson's disease. Under the guidance and supervision of the Food and Drug Administration (FDA) office of Cellular, Tissues and Gene Therapies and the Center for Biologics Evaluation and Treatment (CBER) we are about to begin Phase II trials using this promising cell therapy.

Conclusion

Degenerative and traumatic disorders of the brain represent an enormous burden to the patient, their family and health care providers. The current debate between the embryonic stem cell proponents and those who are opposed to their use distracts

from other avenues with promising outcome, such as adult stem cell therapy. It also overlooks other important issues of resource allocation between basic and clinical research, health insurance, and patient care.

Scientific knowledge has rapidly progressed in the last five years and stem cell research and therapy remains a very promising field for treatment of neurological disorders. In a recent biotechnology industry meeting, a presentation had the approximate title: "*Businesses are from Mars, Academics are from Venus*". What was forgotten there is that patients are from planet Earth and this is what should guide our efforts.

Adult human neural stem cells derived from a patient's own tissue can become a source of replacement neurons, useful for grafting in the treatment of neurodegenerative disorders. With time and adequate support this approach has the potential of making neural stem cell therapy acceptable and available to a large number of patients.

Dear members of the Committee, I appreciate the opportunity to present our results with the use of human adult neural stem cell-derived neurons and to contribute to an honest and objective debate on these important issues.

Adult Neural Stem Cell Therapy for Parkinson's Disease

Michel F. Levesque, MD, FACS, FRCSC
Associate Clinical Professor, Neurosurgery
UCLA School of Medicine
Director of Neural Repair
Cedars-Sinai Medical Center
Los Angeles, California

Stem Cells:Definition

Two properties: 1) self renewing
2) "daughter" cells can differentiate (asymetrical division)

- Totipotent Stem Cell can give rise to any cell type (fusion between sperm and egg/cloning)
- Multipotent Stem cell can give rise to specific cell types along organic system
- Pluripotent Stem Cell can form most cell types but cannot form an entire organism.

2

Embryonic vs Adult Stem Cell

- Embryonic and Adult Stem cells have different molecular properties and different ethical issues associated with their isolation and use
- Isolation easier in embryos than adults
- Both lack clear cellular markers
- Limitations rest in the difficulties of controlling the reconstruction of neural development pathways from ES inner cell mass to post-mitotic mature tissue.

3

Adult Stem Cells

Easiest to obtain: Blood Stem cell from blood sample (CD34), Skin Stem cells from skin biopsy, Neural Stem cells from brain biopsy.

Some Adult Stem Cell lines can be transdifferentiated into new fates: blood cells into neurons, etc…

Unknown behavior of immortalized cell lines, loss of telomerase activity, aging, genetic instability

4

Stem Cells and Human Cloning

Techniques of isolation and manipulation of stem cells similar to techniques involved with cloning mammals.

Currently, cloning, or *somatic cell nuclear transfer (SCNT)* transfers the nucleus (cell's DNA) into a denucleated pluripotent stem cell.

Use of cell line derived stem cells <u>does not</u> mean cloning or duplicating an individual

5

Stem Cell Therapeutics

Theoretically, could replace any cell in the body.

First clinical application, bone marrow reconstruction, to minimize risks of autoimmune, GVHD, with peripheral blood stem cells.

Umbilical cord blood stem cells-banking

Neurological disorders with progressive neurodegenerative or acute cellular loss: Alzheimer's disease, stroke, spinal cord injuries, multiple sclerosis, ALS, epilepsy, and Parkinson's disease.

6

Parkinson's disease

Parkinson's Disease is the most common neurodegenerative movement disorder and afflicts more than 1 million persons in the US (with an estimated prevalence of 1% of the population over 50 years).

Parkinson's disease is associated with a progressive loss of midbrain dopamine (DA) neurons (estimated normally at 500,000 in the substantia nigra compacta(SNc))

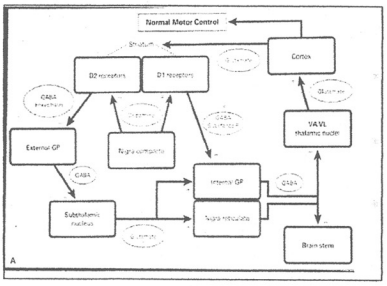
7

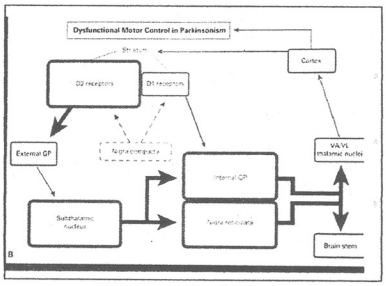
Pathophysiology of Parkinson's Disease

Exact cause remains unknown. Lewy bodies are found in pigmented brain stem neurons. 80% of cell loss before clinical symptoms occur.

Long term medical therapy with levodopa leads to severe secondary motor complications and striatal dysfunction. Neural transplantation aims at replacing the loss of nigrostriatal neurons within the striatum itself.

8





Neurotransplantation

Transplantation of dopamine neuroblasts from fetal mesencephalon restore DA release and ameliorate motor deficits .

Major limitations: ethical, technical variability, poor tissue survival , infection, standardization, quality control… Results of 2 double blind studies:failures

Alternative sources of cells under investigation:
Porcine neuroblasts, retinal cell, embryonic stem (ES) cells and
adult neural stem cells (NSC).

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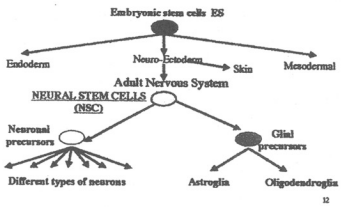
Neural Stem Cell



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Background: Human Adult NSC

1. Multipotent stem cells are found along the ventricular neuroaxis
   Morshead, van der Koy, 1992
   Reynolds and Weiss, 1992
   Lois and Alvarez-Bulla, 1993
2. Proliferate and expand in response to EGF and bFGF
   Morshead et al, 1994, Weiss et al, 1996
3. Continuous neurogenesis occurs in adult rodent dentate gyrus
   Altman and Das, 1965
   Bayer et al, 1982, Kaplan
4. Cortical neurogenesis debate
   Nottebohm, 1986, Gould et al, 1999, Palmer t al, 2000:
   "Where, Oh Where are my Stem Cells!..."

13

Background: Human Adult NSC

5. Neural stem cells isolated from embryonic and adult human brain
   Svendsen et al, 1997, Chalmers-Redman et al, 1997,
   Vescovi et al, 1999, Kukekov et al, 1999

6. Human NSC survive and differentiate into neurons and glia in adult rodent brain.
   Vescovi et al, 1999, Fricker et al, 1999, Carpenter et al, 1999

7. Different population of NSC with regional differences in
   Expression pattern of neurogenic genes (Sommer et al, 1998)
   Transcriptional regulation(Matise and Joyner, 1998)

14

Background: Human Adult NSC

Our Neural Repair Research laboratories isolated human NSC from

- Selective hippocampectomy specimen (Epilepsia 1998)
- Prefrontal neocortex (Soc Neuroscience Abs, 1999), as previously found in rodents, birds and primates.
- Adult NSC are similar to Embryonic NSC in their:
  1. self-renewal potential
  2. ability to differentiate in neural or glial cell lineages (asymmetrical division)
  3. generate neurospheres

Neural Stem Cells (NSC) represent a renewable source of human Neural cells.

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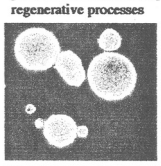
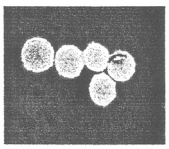
Regeneration Parallels Ontogenesis

Studies of cell division and cell fate demonstrate parallels between developmental cell biology and regenerative processes

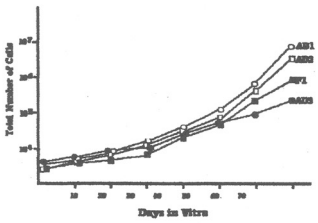


EMBRYONIC NEURAL STEM CELLS



ADULT NEURAL STEM CELLS

Growth of Neural Stem Cells



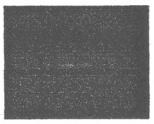
Expression of Regulatory Genes

NSC gene array profiling using cDNA microarrays

Both Adult and Fetal NSC express neurogenic transcription factors (HLH, HD, ZF)

Experimental Results: Adult Human Neural Stem Cells

Adult NSC survive after strital transplantation in 6-OH DOPA rat parkinsonian model, express stable phenotypes, migrate within striatum.



Adult NSC-differentiated DA neurons in rat model can produce DA and correct rotational behavior.

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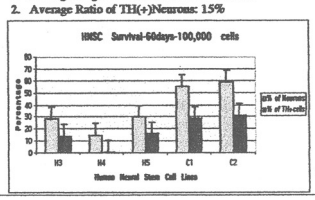
Experimental Results: Survival Human Neural Stem cells

1. Average long term survival of neurons: 31%
2. Average Ratio of TH(+)Neurons: 15%



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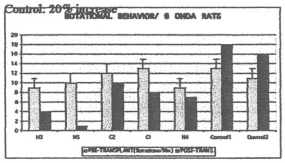
Experimental Results: Functional Human Neural Stem cells

3. Average Functional Recovery after Transplantation:
   Treated: 48% reduction amphetamine induced rotational behavior
   Control: 20% increase



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Methods: From Biopsy to Transplantation

Patient → Harvesting biopsy

Isolation of NSC (20-50 cells)

Propagation of NSC

10^4-10^6 fold increase. Safety, sterility testings, genetic profile, potency assays 4-6 months

Differentiation of cells 5-10 days

Autologous Transplantation

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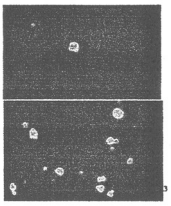
Results: Isolation

Epigenetic stimulation with bFGF (basic fibroblast growth factor) and EGF (epidermal growth factor)



bFGF, EGF, other factors induce larger number of NSC to survive

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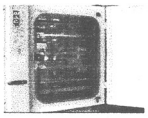
Methods: Cell Expansion

1. Surviving cells grown in serum-free media supplemented with growth factors
2. Neural Stem cells grown as neurospheres in tissue culture flasks
3. Spheres dissociated by mechanical trituration every 2-5 days



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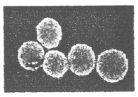
Results: Cell Expansion

NSC propagated as neurospheres in presence of EGF and bFGF for 6 months



Cells reproducibly express Nestin and Musahi mRNA, typical markers of NSC.

After 6 months, NSC exceeded 25 millions

Methods: Cell Differentiation/ Immunostaining

1. Cells dissociated on culture dishes in serum-free medium
   Growth factors and Retinoic Acid, cAMP and GDNF

2. Immunohistochemical staining:
   - ßIII-tubulin antibodies
   - Anti-GAD(GABA)
   - Anti L-glutamate
   - Anti glycine
   - Anti (CHAT)
   - Anti tyrosine hydroxylase (TH)
   - Anti dopa decarboxylase (DDC)

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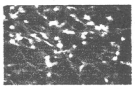
Results: Neural Stem Cell Differentiation

NEURAL STEM CELL LINE	AC2
ASTROCYTES (GFAP +)	49%
OLIGODENDROCYTES (GALC+)	5%
NEURONS (ß III TUBULIN +)	35%



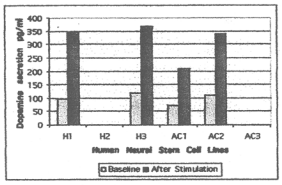
Results: Neural Stem Cell Differentiation II

Differentiated NEURONS from AC2 LINE	35%	
Tyrosine Hydroxylase (+) neurons		15%
Dopa Decarboxylase (+) neurons		13%
GABA neurons		60%
Glutamate neurons		20%
Cholinergic neurons		2%
Glycinergic neurons		3%

28

Results: Dopamine Synthesis

In Vitro Dopamine secretion measured with HPLC analyses Before and After 50mM KCl for 30 minutes



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Phase I Results: Clinical Presentation

Age:	57-year Right H.Male
Disease presentation:	Asymmetrical-Tremor Rigidity-Hypokinesia
Levodopa response:	Positive
Motor Fluctuations:	Some wearing off
Dyskinesia:	None
Disease duration:	11 years
Hoehn and Yahr Stage:	"off" meds:4 "on" meds:2.5
Levodopa daily intake:	600 mg/day

30

Phase I Results: Clinical Presentation

- Clinical Study approved by Cedars-Sinai Medical Center IRB
- Initial surgery:
  - Left Thalamic Stimulator : Sept 1998 Cortical Biopsy(90mm³)
- Cell expansion-Differentiation
- Transplantation procedure:
  - 7 months Post Biopsy
  - Unilateral Left Putamen

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Results: Stereotactic Microtransplantation

- Unilateral Putamen Targets and Trajectories:
  - Six micro-injections, 4mm apart, using modified microsyringe on hydraulic microdrive.
  - Delivery rate of 5 μl/min of cell suspension (1million cells/10min/site)
  - Estimated survival of 600,000 to 1,800,000 cells:
    - 630,000 neurons
    - 93,000 DA neurons
    - 42,000 Glutamate
    - 130,000 GABA neurons

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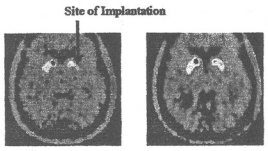
Results: Functional Imaging



PRE-OP 6MO POST-OP

33

Clinical Evaluation

Pre-operative "on"

Post-op 12 months "off" meds/"off" DBS

Post-op 30 months "off" meds/"off" DBS

34

Clinical Evaluation

Pre-operative "on" meds

Post-op 30 months "off" meds/"off" DBS

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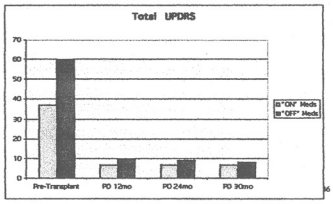
Long Term Outcome Results:UPDRS

- Total UPDRS: 81% improvement "on" / 83% "off"



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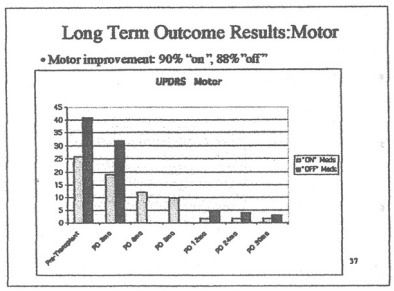

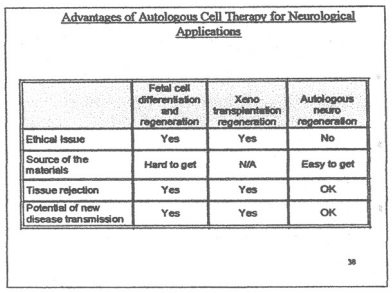

Advantages of Autologous Cell Therapy for Neurological Applications

	Fetal cell differentiation and regeneration	Xeno transplantation regeneration	Autologous neuro regeneration
Ethical Issue	Yes	Yes	No
Source of the materials	Hard to get	N/A	Easy to get
Tissue rejection	Yes	Yes	OK
Potential of new disease transmission	Yes	Yes	OK

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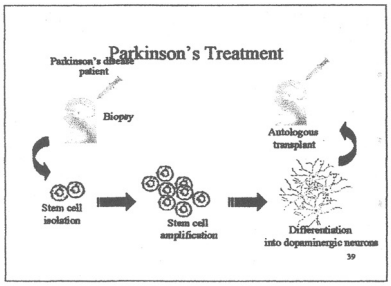

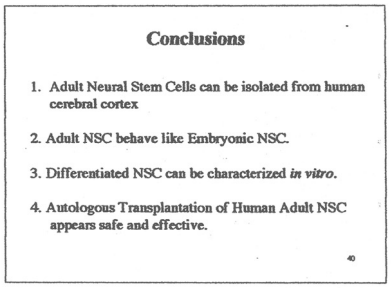

Conclusions

1. Adult Neural Stem Cells can be isolated from human cerebral cortex
2. Adult NSC behave like Embryonic NSC.
3. Differentiated NSC can be characterized *in vitro*.
4. Autologous Transplantation of Human Adult NSC appears safe and effective.

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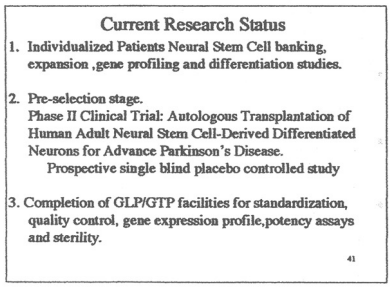

Current Research Status

1. Individualized Patients Neural Stem Cell banking, expansion ,gene profiling and differentiation studies.
2. Pre-selection stage.
   Phase II Clinical Trial: Autologous Transplantation of Human Adult Neural Stem Cell-Derived Differentiated Neurons for Advance Parkinson's Disease.
   Prospective single blind placebo controlled study
3. Completion of GLP/GTP facilities for standardization, quality control, gene expression profile,potency assays and sterility.

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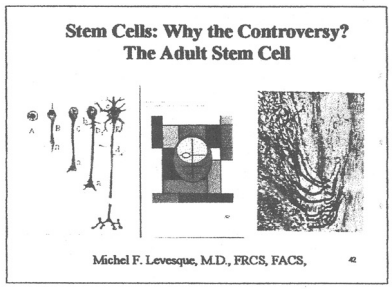

Stem Cells: Why the Controversy?
The Adult Stem Cell

Michel F. Levesque, M.D., FRCS, FACS, 42

Senator BROWNBACK. Thank you, Dr. Levesque. And I look forward, in questioning, to asking you about some of your patients that you've treated. We will have—we will have one patient of yours, I believe, on the second panel.

Dr. LEVESQUE. That's——

Senator BROWNBACK. Is that correct?

Dr. LEVESQUE.—correct.

Senator BROWNBACK. Look forward to that testimony.

Dr. Nelson?

STATEMENT OF JEAN D. PEDUZZI-NELSON, PH.D., DEPARTMENT OF PHYSIOLOGICAL OPTICS, UNIVERSITY OF ALABAMA AT BIRMINGHAM

Dr. PEDUZZI-NELSON. Thank you, Senator Brownback and Members of the Subcommittee.

Senator BROWNBACK. Why don't you get that microphone a little closer to you, if you would? Thanks.

Dr. PEDUZZI-NELSON. It's a pleasure to be here today.

I'd like to tell you about the spectacular results in my patients. Despite what you read in the lab, my patients are all very short and fuzzy, and also commonly known as rats.

[Laughter.]

Dr. PEDUZZI-NELSON. I'm—also have been asked to present the results of Dr. Carlos Lima, in Portugal. He came to my labs and showed me the techniques that he is using in patients, and he asked me to present these results.

For the last 12 years of my life, at the University of Alabama at Birmingham, I have been searching for an effective treatment for spinal cord injury—not just some types of spinal cord injury, but a particular type, severe spinal cord injury, and the chronic condition where, after a year, there is virtually no—there's nothing available for these patients, and there's no further improvement after a year after spinal cord injury.

So I have tried just about everything that's out there. I would try anything that seemed reasonable. And the advantages of the adult stem cells is that you avoid the problems of rejection, you avoid the problems of overgrowth, or tumors, and you avoid all ethical concerns in using adult stem cells. You've heard, from Dr. Levesque, some of his amazing findings in Parkinson's disease. And recently there have been really amazing findings in spinal cord injuries using Dr. Lima's procedure.

It all began—I'm, sort of, going to tell you all this as a story—it all, sort of, started in 1991. Dr. Lima got the idea that maybe, for spinal cord treatment, an effective way of approaching this problem would be the olfactory mucosa. The olfactory mucosa is part of the tissue that lines the inside of the nose. And we knew, at that time, that it has lifelong regenerative capacity, but we didn't know a lot about that tissue. So he started to investigate this tissue. He got autopsy material from 300 patients and actually studied the tissue in different-aged people. He also started an animal trial.

Now, he was at the Hospital Egas Moniz in Lisbon, Portugal, and what he did was a study in guinea pigs. He actually cut the spinal cord. He went back a week later and put some of the animal's olfactory mucosa in this area of the cut spinal cord. And what he found was that some of these animals that received the transplant began to move, and the ones that did not have the transplant continued to drag their legs.

Now, he had very limited facilities at this hospital. As a matter of fact, he took the animals home with him so that he could take care of them. And based on these results, he investigated the possibility of looking into a clinical trial. And what he did was, first he assembled a team of physicians. He's a neurologist and a pathologist. He began working with two neurosurgeons and an ENT doc-

tor. And they formed a team to try to repeat this procedure, but repeat it in patients with chronic severe spinal cord injuries.

And he started with seven Portuguese patients. Some of these patients are two and a half years out right now. And before he started this procedure, they did the procedure in cadavers so they could go through the procedure and work out the details. And he was working with people that have a complete spinal cord injury. That means most of these patients had no sensation, no feeling below the site of injury. They also had no movement. None of the muscles below the site of injury would—had any response, any activity.

And what he found was that all of the patients, the first seven patients that he used this treatment, that there was improvement. Some of them had very dramatic improvement, some of them have limited improvement, but all of them showed improvement—some gain in sensation, some gain in motor activity. One woman, 6 months after the surgery, regained bladder control. There was another woman who, if she had proper facilities, would probably be walking today.

The problem in Portugal was that there was very limited rehab facilities available. So as a next step, he began—he accepted some patients who were interested in this treatment in the U.S. He accepted them to come to Portugal, and some very brave Americans flew over to Portugal and had this surgical procedure done. He had hoped that because there are better rehabilitative facilities in the U.S., he might see even better improvement in these patients.

Now, two of these very brave young women are here today, and you're going to hear their testimony, Laura Dominguez and Susan Fajt. And both of these patients had the surgery about 2 years after their severe spinal cord injury. So, at that period of time, for everyone else, there was no hope of any improvement. Usually patients, after a year, have gotten back any improvement that they would see in their lifetime. And these brave women and their families went to Portugal to have this procedure. And both of them have seen some improvement.

They have—Laura had no feeling and no movement below the level of—in her legs. And after the treatment, now she's able to walk with braces, she's able to point her toes, and has regained some sensation.

Susan, another brave soul who's here today to talk to you, has also been able to do things that the U.S. physicians told her would never happen in her lifetime. She is able to walk with braces. She has regained a certain degree of bladder control. And she has regained feeling in her legs.

So these are very—no, they're not walking into the courtroom unaided, but these are very dramatic findings for someone who, at the time of injury, the doctors told them, "There's going to be no further improvement. There are no treatments available." This is a very hard thing to hear at their young age.

Now, where do we go from here? Obviously, there is further to go in terms of improvement with adult stem cells. In my own research lab, what we've found using this technique, using the olfactory mucosa, was that—in these rats with severe chronic injuries, I got the best improvement that I've seen, trying everything that

was available in the last 12 years that I could try. And so what we need to do next is to either have further improvements—my set of experiments, I'm going to use the olfactory mucosa treatment, and combine it with other treatments so that we can get an even better improvement.

And the other thing that's lacking is that we need a better rehabilitative program in the U.S. The rehabilitation in the U.S. was not designed to handle patients who all of a sudden gained functional connections after several years. And this has to be done very carefully so that there is not injuries. And both of these women have been tremendously helped by their family in going even all over the world to get the best rehabilitative programs developed. And especially Susan and her father, they have developed devices and patented devices, in hopes of getting further improvements that are effective.

Senator BROWNBACK. OK.

Dr. PEDUZZI-NELSON. I hope——

Senator BROWNBACK. Let's—we'll kind of wrap this up, if you can here, very quickly.

Dr. PEDUZZI-NELSON. I'd just—that about summarizes it, that we're hoping to go forward from this point and even have better improvement with adult stem cells.

[The prepared statement of Dr. Peduzzi-Nelson follows:]

PREPARED STATEMENT OF JEAN D. PEDUZZI-NELSON, PH.D., DEPARTMENT OF PHYSIOLOGICAL OPTICS, UNIVERSITY OF ALABAMA AT BIRMINGHAM

"The Truth is not Being Presented"

Thank you Senator Brownback and distinguished Senators of the Subcommittee for the invitation to present to you today. First of all, I would like to commend your subcommittee for bringing to light some of the remarkable advances in adult stem cell research. I have long admired the work of Dr. Michel Levesque in Parkinson's disease and I'm glad that the subcommittee had the opportunity to see the remarkable improvement of his patient with Parkinson's disease who had received a treatment derived from the adult stem cells in his own brain. I am thrilled to hear Dr. Levesque's plan to expand the clinical trials at Cedars Sinai Hospital in California. I know that actually seeing and hearing patients that improved is the strongest evidence of the potential of adult stem cells. *This evidence provides strong refutation to claims about the limited usefulness of adult stem cells* and other sources of cells such as umbilical cord cells. Hearing from patients that actually improved using adult stem cells is more interesting than scientific data and discussions about the stem cell/cloning controversy, but I need your indulgence to present the truth about stem cells and cloning.

1. *Some people* ***naively*** *think that the stem cell controversy is just related to the abortion issues, political party alignment, religious beliefs, or scientific freedom.* However, none of these are the driving force in the effort to promote Federal funding of human embryonic stem cells or human cloning. *The* ***most profitable, not the best, treatment for people is being promoted.*** The main reason for the current controversy regarding human embryonic stem cells & cloning is money. The old statement of *'follow the money'* explains many of the opposing statements made regarding this controversy. It is a superior business plan to have a mass-produced product such as embryonic/fetal/cloned stem cells that can be sold nationwide and has patentable intellectual property.[1] Cloned stem cells derived from embryos with genetic defects represent the possibility of millions in patentable stem cell lines. Adult stem cell therapies are much better for people with diseases or injuries but generate an inferior business plan. In the case of adult stem cells where, in most cases, a person's own cells can be used, one can only develop a procedure that is generally not patentable according to new patent laws. However, the embry-

[1] Marshall, E.(2000) The Business of Stem Cells, Science, 287:1419–1421.

onic/fetal/cloned stem cells can lead to tremendous profits in the short run. Proof of this is the millions of dollars furnished by venture capitalists to help pass a measure that would provide $3 billion for stem cell research in California.[2]

2. *Checks and balances in the form of public policy are needed in society to control greed, especially in those cases where the greater good of the people will be served.* Embryonic/fetal stem cells have the problems of overgrowth, rejection, possible disease transmission, and ethical issues. Tumors have been found in experimental animals[3] [4] and disastrous results have been reported in 2 separate clinical trials[5] [6] using embryonic/fetal tissue/cells. The government should not finance an area of research that is not only dangerous, but also many people view as unethical. Many Americans are against the deliberate destruction of human life. The ban against Federal funding of human stem cells (except for the 67 human stem cell lines) provides a small hope that the financially unprofitable adult stem cell (that are better for people with diseases or injuries) might go forward.
3. *The myth of the availability of countless frozen embryos in fertility clinics is just not true.* To use even one of these embryos would require legal release from the parents that in most states is not easily accomplished. In many cases, it is not that easy to locate the parents especially in the cases of divorce or separation. It is generally assumed that it would not be hard to get parents to agree. However, when it comes to make the final decision, many parents are unsure that they want these potential lives destroyed. Many of the frozen embryos are also not viable. Despite the impressive results with *in vitro* fertilization, recent studies suggest that these children have a higher rate of congenital anomalies and human overgrowth syndrome.[7] [8]
4. The *best way to honor the memory* and work of *President Reagan* is *to not provide Federal funding* for something that President Reagan, if alive today, would *vehemently oppose.* There is no doubt that President Reagan *would not* favor Federal support of research using human embryos. This is very clear from an address given by President Reagan[9]:

   "I, Ronald Reagan, President of the United States of America, by virtue of the authority vested in me by the Constitution and the laws of the United States, do hereby proclaim and declare the *unalienable personhood* of every American, *from the moment of conception until natural death,* and I do proclaim, ordain, and declare that I will take care that the Constitution and laws of the United States are faithfully executed for the protection of America's unborn children."

5. *The often stated advantage that embryonic stem cells can make every cell in body is not an advantage for people with diseases or injuries.* This is only important in terms of a business plan. Science has not worked out all the requirements needed to direct them properly on their path and make sure that they do not develop improperly or become tumors. There are many sources of stem cells in the adult body. Whether each type of adult stem cells can make every different cell type in the body is a mute issue. For example, neurons

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[2] The Ledger.com, Lakeland, FL, Published Thursday, May 20, 2004, "Venture capital money backs California stem cell measure", PAUL ELIAS

[3] L.M. Bjorklund et al.; "Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model," Proc. Natl. Acad. Sci. USA 99, 2344–2349; 19 Feb 2002.

[4] F Nishimura et al.; "Potential use of embryonic stem cells for the treatment of mouse Parkinsonian models: improved behavior by transplantation of in vitro differentiated dopaminergic neurons from embryonic stem cells"; Stem Cells 21, 171–180; March 2003.

[5] Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease. New Engl. J. Med. 344:710–9.

[6] Olanow CW. Goetz CG. Kordower JH. Stoessl AJ. Sossi V. Brin MF. Shannon KM. Nauert GM. Perl DP. Godbold J. Freeman TB. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. [Clinical Trial. Journal Article. Randomized Controlled Trial] Annals of Neurology. 54(3):403–14, 2003

[7] Sutcliffe, A.G, D'Souza SW, Cadman J, Richards, B, McKinlay IA, Liberman B (1995) Minor congenital anomalies, major congenital malformation and development in children conceived from cryopreserved embryos. Hum Reprol. 10: 3332–3337.

[8] DeBaun, E.L Niemitz and A. P. Feinberg (2003) Association of In Vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. Am. J. Hum. Genet. 72: 156–160.

[9] PERSONHOOD PROCLAMATION, National Sanctity of Human Life Day,1988, By the President Reagan, A Proclamation:

(nerve cells) can be derived from cells in the adult brain[10] [11], bone marrow[12], muscle[13] or skin cells[14]. Also there is evidence by Dr. Verfaillie and colleagues at University of Minnesota that stem cells from adults are able to form any cell type in the body.[15]

6. *Several clinical disasters have occurred using embryonic cells/tissue that contain stem cells.* The clinical trials in Parkinson's disease had dramatic differences in their findings depending on the original source of the cells: fetuses or the person's own cells. You've already heard and seen the spectacular results of Dr. Levesque. However, you may not have heard about the clinical trial disasters using embryonic/fetal tissue. When a transplant consists of embryonic/fetal tissue, the stem/progenitor cells are the only cells that survive. A clinical trial was done by Dr. Freed and colleagues[16] in which 19 patients received cells derived from 4 different fetuses from abortions at 7–8 weeks after conception. The patients that were under 60 years showed about a 28 percent improvement in the Unified Parkinson's Disease Rating Scale (UPDRS). However, about 15 percent of these patients showed devastating deterioration at 1 year after treatment that was believed to result from cellular overgrowth. In another clinical trial for Parkinson's disease using embryonic tissue (kept in cold media until transplant), similar results were obtained but the rapid deterioration in some patients was believed to be from rejection of the foreign cells/tissue derived from embryo or fetus.[17]
7. *Terrible catastrophes using embryonic/fetal stem cells are also observed in animal experiments.* In an animal model of Parkinson's disease, rats injected with embryonic stem cells showed a slight benefit in about 50 percent of the rats, but one-fifth (20 percent) of the rats died of brain tumors caused by the embryonic stem cells.[18] This was confirmed in another similar study conducted by a different group of researchers who also found tumor formation in about 20 percent of the rats.[19] In yet another study it was reported that keeping embryonic or fetal stem cells in culture for long periods of time cause genetic mutations and tumor formation when these cells are transplanted.[20]
8. *Cloned human stem cells will not be useful as long as the cloned human embryos are incapable of forming a person.* It often stated that there is no chance of human reproductive cloning because 99.2 percent of cloned embryos can not survive. However, these same faulty cloned embryos are being praised as being a source of valuable stem cells that will advance the cure of genetic disorders. If these cloned human embryos are so abnormal that they almost never can survive in the womb then stem cells derived from them would also

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[10] Vescovi AL. Parati EA. Gritti A. Poulin P. Ferrario M. Wanke E. Frolichsthal-Schoeller P. Cova L. Arcellana-Panlilio M. Colombo A. Galli R. Isolation and cloning of multipotential stem cells from the embryonic human CNS and establishment of transplantable human neural stem cell lines by epigenetic stimulation. Experimental Neurology. 156(1):71–83, 1999.

[11] Song HJ. Stevens CF. Gage FH. Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. Nature Neuroscience. 5(5):438–45, 2002.

[12] Keene CD. Ortiz-Gonzalez XR. Jiang Y. Largaespada DA. Verfaillie CM. Low WC. Neural differentiation and incorporation of bone marrow-derived multipotent adult progenitor cells after single cell transplantation into blastocyst stage mouse embryos. [Journal Article] Cell Transplantation. 12(3):201–13, 2003.

[13] Romero-Ramos M. Vourc'h P. Young HE. Lucas PA. Wu Y. Chivatakarn O. Zaman R. Dunkelman N. el-Kalay MA. Chesselet MF. Neuronal differentiation of stem cells isolated from adult muscle. Journal of Neuroscience Research. 69(6):894–907, 2002.

[14] Toma JG. Akhavan M. Fernandes KJ. Barnabe-Heider F. Sadikot A. Kaplan DR. Miller FD. Isolation of multipotent adult stem cells from the dermis of mammalian skin. Nature Cell Biology. 3(9):778–84, 2001.

[15] Jiang Y. Henderson D. Blackstad M. Chen A. Miller RF. Verfaillie CM. Neuroectodermal differentiation from mouse multipotent adult progenitor cells. Proceedings of the National Academy of Sciences of the United States of America. 100 Suppl 1:11854–60, 2003.

[16] Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease. New Engl. J. Med. 344:710–9.

[17] Olanow, C.W., Goetz, C.G., Kordower, J.H., Stoessl, A.J., Sossi, V., Brin, M.F., Shannon, K.M., Nauert, G.M., Perl, D.P., Godbold, J., *et al.,* 2003. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Annals of Neurology 54:403–414.

[18] L.M. Bjorklund *et al.;* "Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model," Proc. Natl. Acad. Sci.USA 99, 2344–2349; 2002.

[19] F Nishimura *et al.;* "Potential use of embryonic stem cells for the treatment of mouse Parkinsonian models: improved behavior by transplantation of in vitro differentiated dopaminergic neurons from embryonic stem cells"; Stem Cells 21, 171–180; March 2003.

[20] Morshead, C.M., P. Benveniste, N.N. Iscove and D. van der Kooy (2002) Hemapoietic competence is a rare property of neural stem cells that may depend on genetic and epigenetic alterations. Nature Medicine 8:268–273.

abnormal and not useful for research. The big push for cloned stem cells is the possibility of patenting stem cell lines derived from these cloned embryos.

9. *If human cloning is funded to produce cloned stem cells, reproductive cloning could not be prohibited.* Eventually if scientists continue to produce cloned human embryos, it will be possible to form cloned human embryos without defects that will readily give develop to a fully mature person. Although it is often stated that no one would risk the million dollar penalty, the amount invested that resulted in a cloned cat in Texas was 3.7 million dollars. A lot of Americans have less of a moral dilemma with the birth of an individual derived from a clone than creating human life then destroying it for some vague scientific purpose . To my knowledge, there have been no genetic diseases in animals cured with stem cells from clones even though there is no current bans regarding cloning. However, patents of these human stem cells from cloned embryos are likely to bring millions to biotech companies.
10. *Adult stem cells have been shown to make insulin.* Although there are many claims to the contrary, recent studies have shown that stem cells from adults can make insulin. At the University of Florida in Gainsville, Dr. Tang and associates were successful in getting insulin-producing cells from adult bone marrow stem cells. These cell secreted insulin in a controlled manner and reversed diabetes in mice.[21] Also a cell type isolated from bone marrow called MIAMI cells were shown to produce insulin. Insulin producing cells are also produced from embryonic stem cells.[22] However, the stem cells from embryos were inferior to the stem cells from adults because the insulin producing cells from the embryos were not responsive to changing levels of glucose.[23]
11. *Research is **not** being slowed by the current ban on Federal funding of human embryonic/fetal stem cells.* Every clinical trial, new drug, new treatment is based on animal studies. There is no ban on animal embryonic or fetal stem cells or animal cloned cells. There is only a ban on Federal funding of human embryonic or fetal stem cells. As a matter of fact, this ban will bring balance so that adult stem cell research will be further explored even though it is less profitable. There is no ban on using embryonic or fetal stem from animals or private funding of research using human stem cells.
12. *Many alternative treatments besides stem cells are showing progress for treating diseases and injuries.* Before I talk about the progress in adult stem, I would like to mention that in terms of injuries or diseases such as Alzheimer's disease, spinal cord injury, head injury, diabetes, ALS (Lou Gehrig's disease), liver or heart damage and Parkinson's disease, there are *many other alternatives* therapies being scientifically or clinically explored. As a prominent stem cell researcher named Dr. Ron McKay said recently that it was a fairy tale to think that stem cells could help Alzheimer's disease.[24] In the case of diabetes, there is an exciting new drug called liraglutide that seems promising in type 2 diabetes.[25] In recent study using a mouse model of Parkinson's disease, therapeutic immunization using immune cells prevented nerve cells from dying.[26] Progress is also being made in diabetes across the country using islet cell transplants. Recently at my university, University of Alabama at Birmingham, Professor Devin Eckhoff performed an islet cell transplant into a young woman who was totally dependent on insulin shots since age 2. The transplanted cells were obtained from a pancreas of a patient who died in an accident. These transplanted cells immediately began to function and it is hoped that this patient will never have to take insulin shots again.[27] Unfortu-

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[21] Tang, D–Q, L–Z Cao, B.R. Burkhardt, C–Q Xia, S.A. Litherland, M.A. Atkinson, and L–J Yang (2004) In Vivo and In Vitro Characterization of Insulin-Producing Cells Obtained From Murine Bone Marrow Diabetes 53:1721–1732.

[22] D'Ippolito G. Diabira S. Howard GA. Menei P. Roos BA. Schiller PC. Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential. Journal of Cell Science. 117(Pt 14):2971–81, 2004.

[23] Soria B. Roche E. Berna G. Leon-Quinto T. Reig JA. Martin F. Insulin-secreting cells derived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice. [Journal Article] Diabetes. 49(2):157–62, 2000.

[24] Stem Cells An Unlikely Therapy for Alzheimer's Reagan-Inspired Zeal For Study Continues By Rick Weiss, Washington Post, June 10, 2004; Page A03.

[25] *http://www.glucagon.com/liraglutide.htm.*

[26] Benner, E.J., R. L. Mosley, C.J. Destache, T.B. Lewis, V. Jackson-Lewis, S. Gorantla, C. Nemachek, S. R. Green, S. Przedborski, and H.E. Gendelman Therapeutic immunization protects dopaminergic neurons in a mouse model of Parkinson's disease PNAS, 2004.

[27] Black, H. UAB's first islet-cell transplant a success, UAB reporter, vol. 28(27), April 26, 2004.

nately Dr. Eckhoff and his patient were unable to join us today but may testify later in the year.

13. *There has been tremendous progress in adult stem cell research in the last few years.* In another study, adult stem cells transplanted into mice with liver injuries helped restore liver function within two to seven days.[28] Transplantation of stem cells from adult human brain causes myelination to occur in a focally demyelinated spinal cord of the rat.[29] Demyelination is common in spinal cord injury and disease states such as Multiple Sclerosis, and interferes with signal conduction between the neurons. Human cells from adult have been used to treat animal models of disease states. For example, human cells led to functional improvement in animal models of Parkinson's disease using human bone cells[30] or using neural stem cells.[31] Human brain adult stem cells can even be obtained after death[32] so if a person's own stem cells are not used; there are other less objectionable alternatives. Another alternative to the use of embryonic stem cells is human umbilical cord blood. Human umbilical cord blood has the potential to form neurons[33] [34] as well as other cell types.[35] Human umbilical cord blood injected IV caused a functional improvement when injected into experimental animals with traumatic brain injury or stroke.[36] [37] Bone marrow stromal cells from adult rats promote functional recovery after spinal cord injury in rats when given 1 week after injury,[38] even when the cells are injected intravenously.[39] Bone marrow stromal cells also will migrate to site of a head injury when given IV and caused a functional improvement.[40]

14. *There has been progress in treating genetic disorders using adult stem cells or viruses in animal studies but no progress using cloned stem cells to treat genetic disorders in animals.* In the case of genetic defects, there are several other alternatives to cloning. One is gene therapy that has been successfully used in mice[41] and humans. More recently stem cells have been used as vehi-

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[28] Y.-Y. Jang, M.I. Collector, S.B. Baylin, A.M. Diehl, S.J. Sharkis, Hematopoietic stem cells convert into liver cells within days without fusion. Nature Cell Biology: 6, 532–539, 2004.

[29] Akiyama Y; Honmou O; Kato T; Uede T; Hashi K; Kocsis JD: Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. Exp Neurol 167:27–39, 2001.

[30] Hou LL. Zheng M. Wang DM. Yuan HF. Li HM. Chen L. Bai CX. Zhang Y. Pei XT.[Migration and differentiation of human bone marrow mesenchymal stem cells in the rat brain].Sheng Li Hsueh Pao—Acta Physiologica Sinica. 55(2):153–9, 2003.

[31] Liker MA. Petzinger GM. Nixon K. McNeill T. Jakowec MW.Human neural stem cell transplantation in the MPTP-lesioned mouse. Brain Research. 971(2):168–77, 2003.

[32] Palmer TD. Schwartz PH. Taupin P. Kaspar B. Stein SA. Gage FH. Cell culture. Progenitor cells from human brain after death. Nature. 411(6833):42–3, 2001.

[33] Sanchez-Ramos JR. Song S. Kamath SG. Zigova T. Willing A. Cardozo-Pelaez F. Stedeford T. Chopp M. Sanberg PR. Expression of neural markers in human umbilical cord blood. Experimental Neurology. 171(1):109–15, 2001.

[34] BuzaAska L. Stachowiak E. Stachowiak M. DomaAska-Janik K.Neural stem cell line derived from human umbilical cord blood—morphological and functional properties. Journal of Neurochemistry. 85 Suppl 2:33, 2003.

[35] Goodwin HS. Bicknese AR. Chien SN. Bogucki BD. Quinn CO. Wall DA. Multilineage differentiation activity by cells isolated from umbilical cord blood: expression of bone, fat, and neural markers. Biology of Blood & Marrow Transplantation. 7(11):581–8, 2001.

[36] Lu D. Sanberg PR. Mahmood A. Li Y. Wang L. Sanchez-Ramos J. Chopp M. Intravenous administration of human umbilical cord blood reduces neurological deficit in the rat after traumatic brain injury. Cell Transplantation. 11(3):275–81, 2002.

[37] Sanberg PR. Chopp M. Willing AE. Zigova T. Saporta S. Song S. Bickford P. Garbuzova-Davis S. Newman M. Cameron DF. Sanchez-Ramos J.Potential of umbilical cord blood cells for brain repair. Journal of Neurochemistry. 81 Suppl 1:83, 2002.

[38] Hofstetter CP. Schwarz EJ. Hess D. Widenfalk J. El Manira A. Prockop DJ. Olson L. Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. Proceedings of the National Academy of Sciences of the United States of America. 99(4):2199–204, 2002.

[39] Akiyama Y. Radtke C. Honmou O. Kocsis JD. Remyelination of the spinal cord following intravenous delivery of bone marrow cells. [Journal Article] GLIA. 39(3):229–36, 2002.

[40] Lu D, Mahmood A, Wang L, Li Y, Lu M, Chopp M.(2001) Adult bone marrow stromal cells administered intravenously to rats after traumatic brain injury migrate into brain and improve neurological outcome. Neuroreport 12:559–63.

[41] Shen JS. Watabe K. Ohashi T. Eto Y. Intraventricular administration of recombinant adenovirus to neonatal twitcher mouse leads to clinicopathological improvements. Gene Therapy. 8(14):1081–7, 2001.

cle to deliver genes to the brain.[42] [43] [44] [45] Another valuable source of research into genetic disorders is adult stem cells that can obtained from patients with genetic defects or strong genetic background to develop particular diseases.

15. *Tremendous progress has been made using adult stem cells in clinical trials in treating diseases and injuries.* You have already heard about the wonderful results of Dr. Levesque at Cedars-Sinai in treating Parkinson's disease using a person's own stem cells. I would now like to describe the use of olfactory mucosa in the treatment of spinal cord injury.

Olfactory Mucosa

The olfactory mucosa lines the upper nasal cavity. It all starts with a brilliant neurologist from Portugal named Dr. Carlos Lima. He is also a pathologist that has published on the olfactory system and studied a collection of hundreds of olfactory mucosas from cadavers. In 1991 which is the year before stem cells were first discovered in the brain, he decided to explore the potential of olfactory mucosa in the treatment of spinal cord injury because the olfactory system was the only system in the adult nervous system that regenerates. With very limited facilities, Dr. Lima began a study using 14 guinea pigs in which the spinal cord was completely cut (transected). A week later, he implanted a piece of olfactory mucosa from the nose of that animal. He noticed that the guinea pigs that received the transplant were able to walk much better than the guinea pigs without the transplant. When he examined the spinal cords, the guinea pigs that improved showed tissue bridging between the 2 cut ends.

We now know that there are several advantages to the olfactory mucosa. The major advantage of the olfactory mucosa is its lifelong continual regenerative capacity including the production of nerve cells. It is also accessible with minimally invasive techniques. The olfactory mucosa contains 2 cells types that we know help repair the nervous system: stem cells and olfactory ensheathing cells. The olfactory ensheathing cells encourage the growth of nerve cell processes (axons) and promote the myelination (covering on nerve cell processes that speed up the signal between neurons). Removal of part of the mucosa causes no permanent damage to olfaction (smelling). Problems of rejection, overgrowth, disease transmission, and ethical issues can be avoided because a person's own olfactory mucosa can be used.

When Dr. Lima visited my lab, he showed me and my collaborator, Dr. Jay Meythaler, his procedure. I began a rat study with that was supported by the Foundation for Neural Repair. In this study, we compared a wide variety of treatments in rats with chronic, severe spinal cord injury. The person doing the functional testing was unaware of the treatment that the rat received. The average functional scores of the 6 weeks prior to the treatment period were compared to the average functional scores of weeks 5–10 after treatment. The improvement was greatest in the rats with the olfactory mucosa transplants. Also improvement was found in the rats that received bone stromal cells IV injections. This improvement with the olfactory mucosa cells is the greatest improvement that I have found in the 12 years of evaluating treatments for severe spinal cord injury. Below is the graph of the results:

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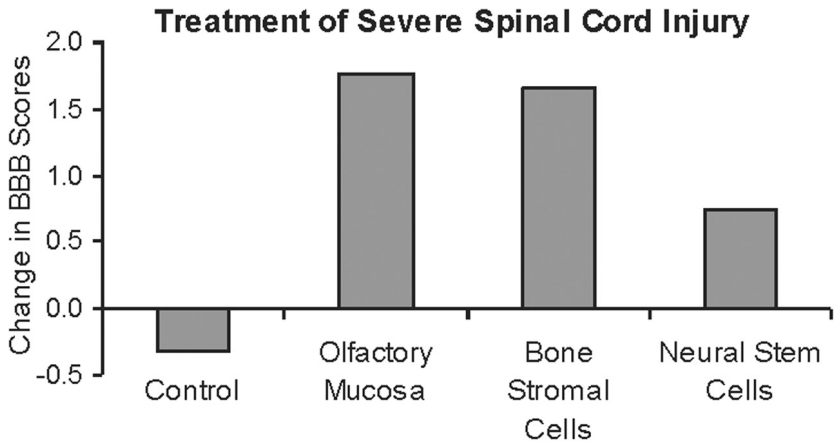
[42] Schwarz EJ. Reger RL. Alexander GM. Class R. Azizi SA. Prockop DJ. Rat marrow stromal cells rapidly transduced with a self-inactivating retrovirus synthesize L–DOPA in vitro. Gene Therapy. 8(16):1214–23, 2001.

[43] Nakano K. Migita M. Mochizuki H. Shimada T. Differentiation of transplanted bone marrow cells in the adult mouse brain. Transplantation. 71(12):1735–40, 2001.

[44] Park KW. Eglitis MA. Mouradian MM. Protection of nigral neurons by GDNF-engineered marrow cell transplantation. Neuroscience Research. 40(4):315–23, 2001.

[45] Ehtesham M. Kabos P. Gutierrez MA. Chung NH. Griffith TS. Black KL. Yu JS. Induction of glioblastoma apoptosis using neural stem cell-mediated delivery of tumor necrosis factor-related apoptosis-inducing ligand. Cancer Research. 62(24):7170–4, 2002.



Excellent graft integration and reduction in lesion size were observed in the spinal cords of rats receiving the olfactory mucosa transplants.

Clinical Trials by Dr. Carlos Lima and Colleagues in Portugal

Based on the animal results, Dr. Lima proposed a clinic trial in Portugal. A team of physicians was formed that was headed by the neurologist and pathologist, Dr. Carlos Lima and included the Neurosurgeon, Dr. José Pratas-Vital, an Otolaryngologist, Dr. Pedro Escada; and a Neurosurgeon, Dr. Armando Hasse-Ferreira. As a first step in this procedure, the team of doctors did numerous sham operations on cadavers to master the technique. The whole procedure was reviewed and approved by the Ethical Committee and Administration of the Hospital Egas Moniz-Lisbon. *Dr. Lima and his team of doctors have requested that I present the results of the study.* All of the people were treated in Portugal between 6 months and 6 years after their injury. The normal improvement, if any, that occurs after spinal cord injury takes place in the 6 months to a year after injury so these patients were treated at a time when no further improvements are expected. In this procedure, the area of the spinal cord damage is exposed surgically in patients with severe spinal cord injuries. Then a small piece of olfactory mucosa in the upper part of nose is removed from that same patient. The olfactory mucosa is then rinsed, cut in small pieces and placed in the spinal cord. Below are the MRIs of one of the patients from Portugal named Ana: The area that the arrow is pointing at on the left is the MRI before the treatment. There is a cystic cavity that appears white. On the right is the MRI after the treatment, the arrow points to the same area that is almost completely filled.

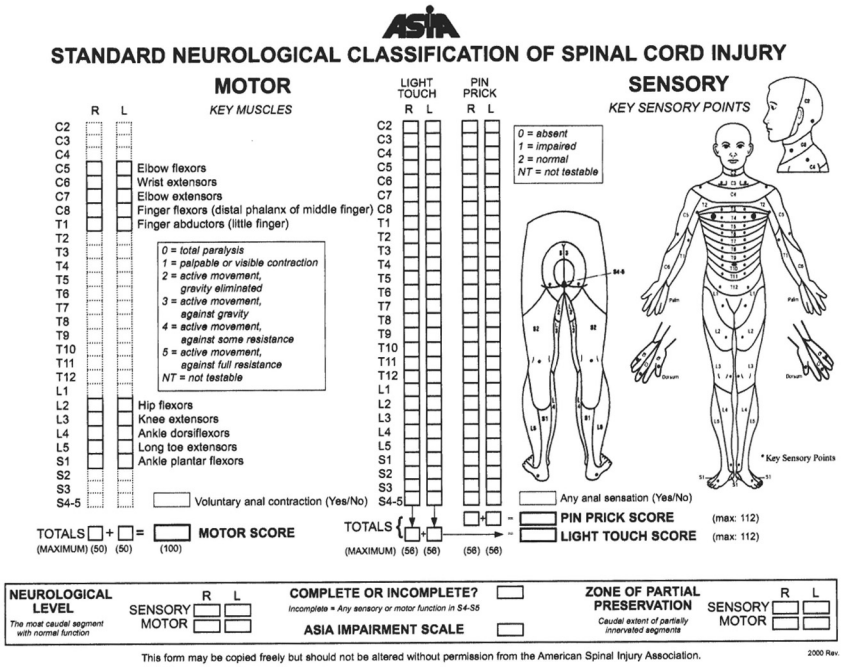
Before Treatment

After Olfactory Mucosa Transplant

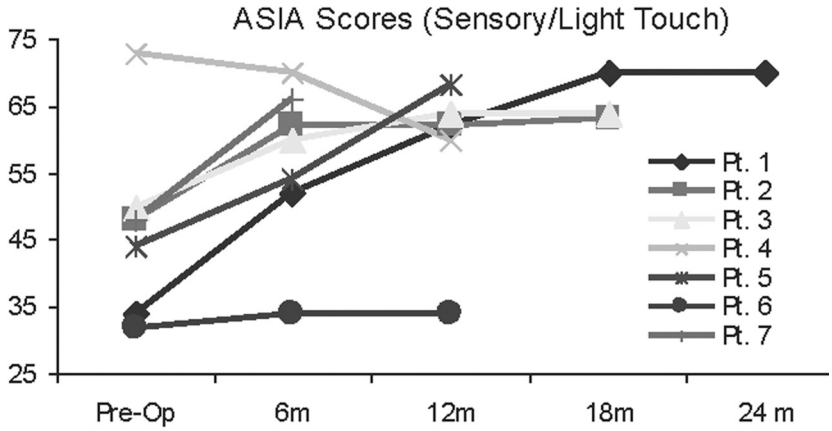
It appeared that as in the animal studies, there was bridging of the injury. However, it is impossible to tell that there was tissue in a living individual but it is probable.

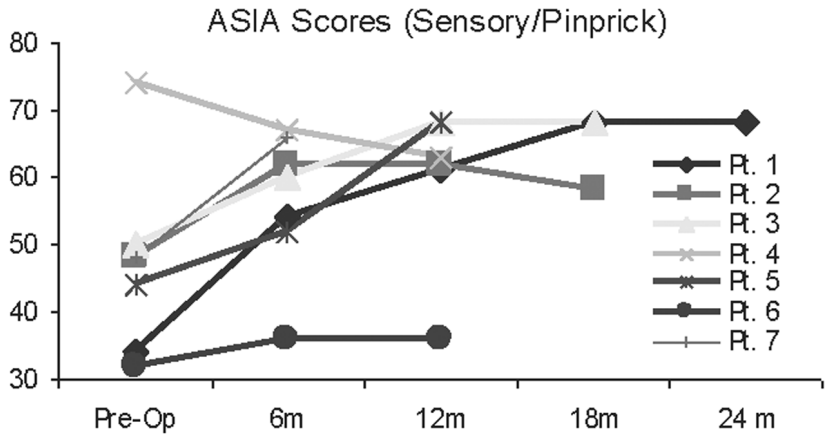
All of the patients tolerated well the surgery. Olfaction returned to normal by 3 months after the surgery. All of the patients showed improvements. One of the patients regained bladder control at 15 months after the surgery. Regaining bladder control is extremely important to those patients with spinal cord injury. All but one of the patients gained feeling in some areas of their body where they previously had no feeling. All of the patients gained the ability to move certain muscles that they could not move before the olfactory mucosa treatment.

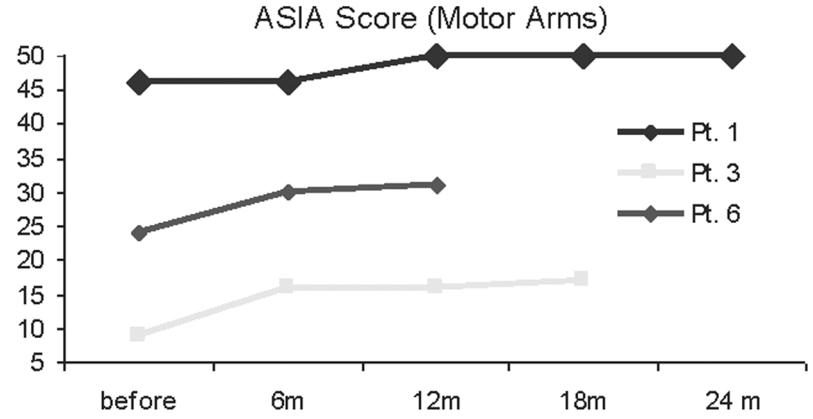
In order to quantify the changes as a result of the treatment, an evaluation called the ASIA neurological exam is used. As you can see from this diagram below, points are given for each part of the body that has sensation or movement. A normal person has 112 on the sensory scale and 100 on the motor scale. The results of his first seven Portuguese patients that were treated from 6 months to 6 years after injury are presented using the ASIA neurological exam.

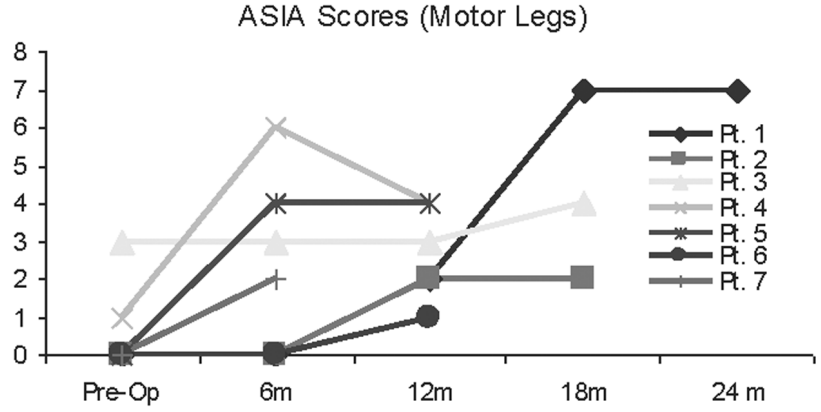


The beginning score (Pre-Op) is the score before receiving the olfactory mucosa treatment and is shown on the far left. The results after the olfactory mucosa treatment by Dr. Carlos Lima and colleagues are recorded at every six months after surgery. The patients were operated at different time so some of the patients only have a few scores so far. An increase in score means that there is an increase in sensory or motor function.









In summary, all of his patients that were treated with the olfactory mucosa showed some improvement. However, most of the patients did not have access to

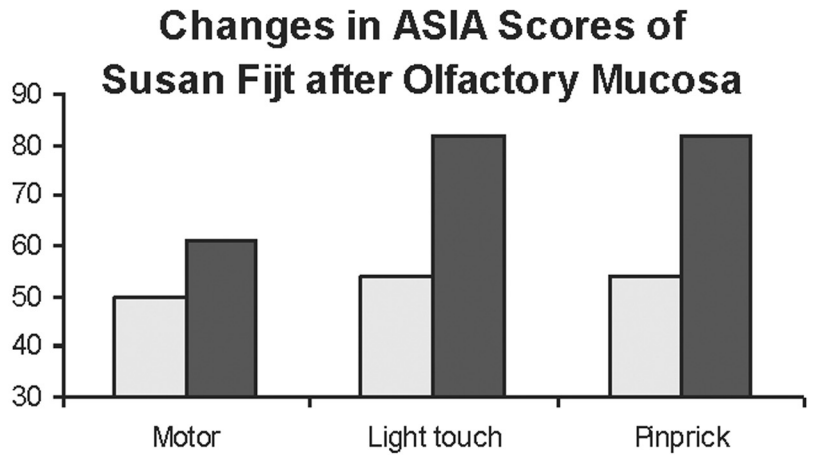
the best rehab facilities. This was very frustrating because it appeared that the patients would improve further if only better rehab facilities were available.

In hopes of the patients being able to have access to better rehab facilities, several American patients that had requested the treatment were enrolled in the clinical trial. Some of these patients were carefully evaluated by physicians in the U.S. before and after the olfactory mucosa treatment in Portugal. Two of these brave young women are here today to tell about their experiences.

Results in Two Americans after Olfactory Mucosa Treatment by Dr. Lima

Laura Dominguez had her accident on July 3, 2001. She had no movement of her legs or hips and no feeling below her collarbone. Laura, was 18 years old, tetraplegic with a lesion at the 6th cervical level that was 2 cms long. The lesion was mixed glial and connective tissue produced by a contusion and laceration. She went to a variety of excellent rehabilitation centers including Dr. John McDonald's in St. Louis and Project Walk in California. These centers helped her improve her upper body strength but still she could no move her hips, legs or feet and she had no feeling in these areas. In the U.S., Dr. Steve Hinderer and The Rehabilitation Institute of Michigan (currently headed by Dr. Jay Meythaler, associated with Detroit Medical Center and Wayne State University) began to look into the potential of Dr. Lima's procedures on the encouragement of Fred Nader whose daughter had a spinal cord injury. After almost 2 years after her accident, Laura and her family decided to go to Portugal to have the olfactory mucosa surgery performed by Dr. Lima and his team of doctors in March of last year. After her surgery, she regained some sensation and motor control of certain muscles. She is now able to point her toes. With braces, she is able to walk some distance. Although she has made remarkable improvements, a rehabilitation program that is actually tailored to these types of patients needs to be developed. Laura has received some help in developing a vigorous rehabilitation program from a talented karate instructor named Ivan Ujeta. Aquatherapy (water therapy) has proven to be particularly helpful. However, Laura and her family feel that rehabilitation programs need to be developed.

Susan Fijt was in a car accident on Nov. 17, 2001. The spinal cord lesion was at thoracic level 7 and 8 and was about 3 cms long. Susan was an ASIA A (complete). She had no voluntary or sensory below her level of injury. Susan had no sensory or motor on S4–S5 segments. At about 21/2 years after her injury, Susan went to Portugal to have the surgery performed by Dr. Lima and his team in June of last year (2003). She started to have real gains around 6 months after the olfactory mucosa treatment with increased bladder control, sensory recovery and first movements of her thigh muscles. Susan and her father looked for the best rehab program; however, it seemed that optimal rehabilitation program has yet to be designed. Her father, John Fijt with her help began to develop and patent devices such as a cross-trainer, standing wheel-chair (Venus craft), and camel wheel-chair (lowers or raises to facilitate going into and out of the pool) that would help her progress. She gained voluntary movements on thigh muscles. In May at Dr. Albert Bohbot in France, Susan got more strength on these muscles and began walking on a walker with braces on legs. The graph below shows the changes in her ASIA scores.



The story of these 2 courageous young women dramatically shows the progress of adult stem cells and tissue and the need for further research into the less profitable, but more beneficial, direction of adult stem cells. Further work is needed to improve this technique, with the addition of other treatments including a rehabilitation program that will maximize the functional improvement.

My statements represent my scientific viewpoint and not the opinion of The University of Alabama at Birmingham which has no official opinion on this topic. A special note of thanks to Dr. Joseph Horton at The University of Alabama at Birmingham who arranged for the digitization of some of the MRIs on very notice.

Senator BROWNBACK. Very good.

Dr. Weissman, you've testified many times, and I'm delighted to have you back again.

STATEMENT OF IRVING WEISSMAN, M.D., KAREL AND AVICE BEEKHUIS PROFESSOR OF CANCER BIOLOGY, DIRECTOR OF THE INSTITUTE OF CANCER AND STEM CELL BIOLOGY, AND PROFESSOR IN THE DEPARTMENTS OF PATHOLOGY, DEVELOPMENTAL BIOLOGY, AND BIOLOGY, STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. WEISSMAN. Thank you.

So my name is Irv Weissman. I'm an M.D. I'm Director of the Stanford Institute of Cancer and Stem Cell Biology and Medicine. I'm a stem cell biologist.

We purified blood-forming stem cells first from mouse, and later isolated human brain-forming stem cells. Blood-forming stem cells regenerate the blood in the immune systems after radiation exposure or after high-dose cancer therapies.

I cofounded Cellerant, Inc., to transplant human blood-forming stem cells to regenerate the blood in these patients, and also to replace genetically defective blood systems with healthy stem cells in diseases such as sickle cell anemia and the autoimmune diseases. We have shown, in diabetic mice, that a blood-forming stem cell transplant from a genetically resistant donor permanently blocks the autoimmune reaction that kills the insulin-producing cells.

Such stem cell transplants also block autoimmune reactions in mouse models of Multiple Sclerosis and Lupus, to name a few. And the hosts whose immune systems come from a stem cell donor can, for life, accept the tissue, organ, or cell transplants from that donor without any anti-rejection drugs. That is, the donor system repopulates the body. It won't reject the host, and it won't reject itself.

I also cofounded a company called Stem Cells, Inc., to treat neurodegenerative diseases, the kind that Dr. Levesque was just talking about, by transplanting brain stem cells, adult-type tissue brain stem cells. The company has promising data in treating mice that have a mouse model of a human fatal childhood neurodegenerative disease—that one's called Batten's disease—and mice with spinal cord injury, and a variety of demyelinating diseases. We are also currently testing these cells in a mouse model of human Alzheimer's disease with a group in Montana. In all of these tests, only small numbers of purified stem cells are required to give lifelong and robust tissue regeneration.

I do not have any connection with any commercial entity in the area of embryonic stem cells or nuclear-transfer-produced pluripotent stem cells. While I'm probably the strongest advocate

of adult-tissue stem-cell approaches, I'm also the strongest critic of unproven stem cell discoveries.

You may have heard that one kind of adult-tissue stem cell can easily, robustly turn into any adult tissue. I was especially excited with claims that the blood-forming stem cells, the ones that we discovered, could regenerate injured hearts or brains or muscles or insulin-producing cells. But when we tested these notions directly and experimentally with purified blood-forming stem cells, or any bone marrow cells, the blood-forming stem cells only made blood. They did not regenerate the heart, the brain, the muscle, or insulin-producing islets. So we were very disappointed.

What about embryonic stem cells from in vitro fertilization clinics, and nuclear-transfer stem cells? I'll call them NT stem cells. The current embryonic stem cells allowed by President Bush to be studied with government funding are important in studying human developmental biology, but cannot tell us about human inherited diseases or be used in transplant therapies.

NT stem cells are made, for example, by taking a skin cell, putting it into an egg that lacks chromosomes—they had it removed—stimulating it to divide to form a stage at which you can make these pluripotent stem cell lines, so they come from the donor nucleus. These stem cell lines develop in a test tube into every cell type in the body. We can do it in mice.

If the skin cell comes from a donor with a Bubble Boy immunodeficiency—you remember John Travolta in the movie?—the mouse donor of that stem cell gives rise to a stem cell line that redevelops that disease. If it comes from a cancer stem cell—say, a melanoma—the stem cell line redevelops the melanoma, whether it's in a mouse or in a test tube. Perhaps even cells from a complex inherited disorder, like Lou Gehrig's disease, will someday make stem cell lines that undergo motoneuron degeneration in the lab. These are scientific discoveries now present in mouse labs.

There's something in common between virtually all human genetic diseases and all human cancers. That is, although we are finding out which genes seem to be involved, thanks to the Human Genome Project mapping genes that correlate with the disease, but we don't know in which cells and how the disease develops. And to find treatments and cures, that is just what we must know. We must understand how genetic defects in humans that lead to disease cause that disease if we're going to get anywhere to try to cure these diseases.

There's a promising field publicly called therapeutic cloning, where you start with a cell from you to make a stem cell line transplantable to you. That field is just at the beginning, but if we can make—if the scientific community could make progress, it has enormous therapeutical potential also.

So we come to the problem. It would be certainly of great medical benefit to open these platform technologies to produce predefined stem cell lines. Imagine if we had, and could distribute to the best and the brightest, a juvenile diabetes stem cell line from a juvenile diabetes patient, or a Lou Gehrig's disease stem cell line that recapitulates that disease. Today, the best and brightest biomedical experts in the U.S. cannot receive or use such cell lines because they would have been made after August 9, 2001. It doesn't make

sense to me. What makes even less sense is the bill proposed to criminalize all aspects of producing, studying, and even developing treatments using NT stem cell technology.

If this turns out to be like the recombinant DNA example 25 years ago, which we regulated rather than banned, tens of thousands of born human lives are at stake. In my view, whoever of you acts to ban this research is responsible for the lives it could save. I know that's a hard statement, but I believe that. As an M.D., I took an oath to try to save those kinds of lives.

Banning research for an ideology is just not the American way. It's more like Russia, which, in the 1930s, banned Darwinian genetics, Darwin's genetics, in favor of Lamarckian approaches espoused by Stalin's advisor, Lysenko. We all know what happened there. Some scientists were fired, others jailed, and others emigrated to the U.S. to set up the U.S. as the world leader in genetic and biological research. For at least 50 years, Russia didn't produce any advances in genetics. Their crops failed, and few premier Russian geneticists were trained. The biotechnology industry passed them by, and Russian patients suffered. Fifty years.

I beg you to think hard about what you do before you enact the first ideological ban of biomedical research in the history of the U.S. Separate the issues and ban reproductive cloning of humans, because that needs to be done to protect patients. That's a whole 'nother subject.

There has to be a stem cell research bill that funds and regulates this kind of research. We want it regulated. We want it regulated like recombinant DNA. We want to make sure no rogue labs take advantage of it. Don't put us on the sidelines while we read of advances in South Korea, the UK, Singapore, Israel, or China. Remember, nearly every American family has a family member or a close friend with one of the diseases this technology could help.

I thank you.

[The prepared statement of Dr. Weissman follows:]

PREPARED STATEMENT OF IRVING WEISSMAN, M.D., KAREL AND AVICE BEEKHUIS PROFESSOR OF CANCER BIOLOGY, DIRECTOR OF THE INSTITUTE OF CANCER AND STEM CELL BIOLOGY, AND PROFESSOR IN THE DEPARTMENTS OF PATHOLOGY, DEVELOPMENTAL BIOLOGY, AND BIOLOGY, STANFORD UNIVERSITY SCHOOL OF MEDICINE

My name is Irv Weissman. I received my MD degree in 1965 from Stanford, where I am now the Karel and Avice Beekhuis Professor of Cancer Biology, Director of the Institute of Cancer and Stem Cell Biology and Medicine, and Professor in the Departments of Pathology, Developmental Biology, and by courtesy, Biology; I attach my full CV for your information. I was also Chairman of the National Academies (NAS, NAE, IOM, NRC) Panel on the Scientific and Medical Aspects of Human Reproductive Cloning, which also dealt with the issue of human pluripotent and human embryonic stem cell research.

My field of research is adult tissue stem cell biology. We were first to isolate any adult (or tissue) stem cell—the mouse hematopoietic (blood-forming) stem cell (HSC), followed by the human HSC, the human CNS (brain cell forming) stem cell, and most or all blood system committed progenitors in mouse and man.

I am cofounder of the following adult or tissue stem cell companies—Stem Cells, Inc (mainly human CNS stem cells) and SyStemix, Inc (human HSC). SyStemix released the stem cell service transplant functions to Celtrans, now Cellerant, Inc, to deliver human HSC and blood system progenitors to patient populations. I own stock in Stem Cells, Inc, and Cellerant, Inc and am a Director of both companies. These relationships have been disclosed to Stanford, and subjected to extensive review to assure avoidance of conflicts of interest, including the establishment of over-

sight committees, when indicated . I have no commercial or advising relationship with any for profit entity in the fields of human *embryonic stem cells or nuclear transfer (NT) to produce human pluripotent stem cells* .

As a scientist in *adult tissue stem cell* research I have played a role in helping define the field, and in that role pointing out errors or misstatements or less than rigorous research. Stem cells are defined as cells that can divide to give rise to new stem cells, by a process we call *self-renewal;* and also progenitors and mature tissue cells, in a process called *differentiation.* The clonal progeny of a single HSC include HSC and all blood cells . The progeny of brain stem cells include more brain stem cells, as well as the differentiated brain cell types.

Any use of the term *stem cell* must have the characterization of the cell (at the single cell level), include a proof of the capacity for self-renewal and differentiation. These are generally accepted definitions of the field by the leaders in the field of stem cell biology. However, much of the testimony you have heard in the past and will continue to hear have fallen short of this standard. All those who have testified, are testifying and will testify should be held to that standard. So far, isolated tissue stem cells upon transplantation to appropriate hosts results in *robust* regeneration of all the kinds of cells in the tissue from which the stem cells were isolated, almost always requiring only small cell numbers.

Many clinically important avenues have been opened by this type of adult tissue stem cell research. For example, human HSC (blood-forming stem cells) have been isolated from patients with widespread cancers, in which the cancer cells and the HSC are intermixed in blood and bone marrow; the *isolated blood-forming stem cells* are no longer contaminated with cancer cells. In 3 early phase clinical trials it was shown that these pure HSC's regenerate the blood forming system of patients treated with massive doses of chemotherapy; the chemotherapy is used to kill as many cancer cells in the body as possible, and the HSC transplants (that are not cancer cell contaminated) restore blood formation as efficiently as any bone marrow transplant, but without giving back cancer cells to the patient. In mouse models of human disease we have been able to replace the disease-causing blood forming system with a blood-forming system that resists that disease; an example is mouse type 1 (juvenile) diabetes, where a timely transplant permanently stops the autoimmune attack on the insulin-producing pancreatic cells. Other such blood diseases include sickle cell anemia, thalassemia, severe-combined immunodeficiency (the so-called bubble boy disease), and the mouse model of lupus, among many others.

In addition, the replacement of the blood forming system of mouse strain A with HSC from mouse strain B has allowed the permanent transplantation of heart, or skin, or insulin-producing islet cells from B donors to A hosts without any subsequent immunosuppression. Nuclear accidents and exposure to other blood-destroying agents can only be treated with HSC or blood progenitors.

We are now exploring in mouse models the utility of brain-forming stem cells in various neurodegenerative disorders, including spinal cord injury, inborn errors such as Batten's Disease, Niemann-Pick, etc, as well as Alzheimer's, Lou Gehrig's, Parkinson's, and Huntington's Diseases, and even cerebral palsy. All of this research is at an early stage, and we cannot predict which, if any indications will be ameliorated or cured. You might think that I am biased. But science is a field that demands independent replication, so any bias I have will be tested empirically. For all of these reasons, you should know that I am *the strongest possible advocate for tissue (adult) stem cell research and therapies,* but I am also the strongest critic of inappropriate extrapolations and inadequate claims from 'stem cell' therapies that are unproven. We have only found adult tissue stem cells so far for a few tissues, and much discovery research will be needed to find others, if they exist.

A central issue in this hearing is whether adult or tissue stem cells of one type, can change their fate to that of another tissue, for example blood-forming stem cells to brain, or heart, or skeletal muscle, by *transdifferentiation.* When the first reports of HSC transdifferentiation to regenerating heart cells, or brain cells, or liver cells, or skeletal muscle cells were reported I was excited that the HSC we had isolated might have much broader clinical uses than we had initially envisioned. So we embarked on experiments to repeat the original findings., hoping to make them better understood and easier and more efficient by improving the processes involved. But we found that we could not confirm blood-forming stem cells giving rise to brain, or heart, or liver, or skeletal muscle in a robust fashion. I attach several of our papers that represent attempts to reveal normal tissue regeneration using stem cells from distinct tissues. In brief, we could not substantiate the claims; only rare (less than 0.1 percent) of any damaged and repairing tissues (heart, leg muscles, brain) had donor cell markers in regenerating host tissues. All of these rare cases of donor markers in host cells turned out to be due to a very rare event that can occur in tissue damage—the fusion of donor blood cells used in mopping up damaged areas

with resident tissue cells that survived the damage, not the transdifferentiation of blood-forming stem cells to brain, or heart, or muscle, or liver. These findings, like many in biomedical sciences, turned out to be due to different interpretations of similar findings, or due to some consistent misleading methods to reveal the underlying phenomena. All of us in the life sciences have experienced the disappointment that what we thought was a major finding turned out to be due to something other than we suspected at the time. Luckily, the practice of studying particular subjects in several independent labs provides a continually self-correcting aspect to our field. Moreover these cell fusions were rare and not robust events leading to massive tissue regeneration. While with added experiments these rare cell fusion events may turn out to be of some biological interest, *none of us should expect that such cells provide a means to regenerate different tissues and organs.* On the other hand, adult tissue stem cells (as described above) can lead to robust regeneration, but only of the tissue from which they came.

These findings (and others) have led us to posit several requirements, all of which should be met before one begins clinical trials in stem cell research, and of course before the press should pronounce preliminary results as conclusions and before legislative bodies should base their decisions on these findings as facts. These are:

(1) The original research finding must be published in a peer-reviewed journal . . . but that is not enough.

(2) The experiments as reported must be replicated in several independent laboratories . . . but that is not enough.

(3) Any way you investigate the phenomenon you should be able to come to the original conclusions . . . but that is not enough.

(4) Preclinical (*i.e.,* animal) experiments should show that the injected cells can robustly regenerate the damaged tissues in a timely fashion before they should be considered for human clinical trials.

About 3 years ago I was asked by the Presidents of the National Academies (National Academy of Sciences, National Academy of Engineering, National Research Council, Institute of Medicine of the National Academies) to lead a panel to gather information and provide a thorough, objective report on two related issues, the *scientific and medical aspects of human reproductive cloning,* and the use of *nuclear transfer technology to produce human pluripotent stem cell lines.* They chose the panel to provide experts in the related fields of life sciences, medicine; and medical ethics as it applies to human participants in medical research trials or experiments. We all agreed that we had not made up our minds on these subjects beforehand; that we would gather as much data as could be obtained; that we would have a public meeting of experts and would-be practitioners of both fields; and that we would keep our deliberations and thoughts confidential until we had heard and read all of the relevant data and had discussed them thoroughly, and prepared our consensus report for public disclosure. I have appended the executive summary of that report.

In brief, we found from very extensive animal studies that a clonal embryoid blastocyst (I call it embryoid because it was not generated by sperm-egg fertilization, but by transfer of a body cell nucleus into an egg whose own nucleus had been removed) implanted into the uterus of a hormonally prepared female of the same species only results in a live birth in 0.8 percent of the cases, and even in those cases most died soon after birth. More ominously, unlike a miscarriage that is over in the first trimester without measurable morbidity or mortality, these reproductive clones aberrantly died throughout pregnancy, often taking the mother with them. This would clearly be an unacceptable risk for humans, as codified in the medical ethics literature, *e.g.,* the Nuremburg code. Accordingly, we concluded, unanimously, that there should be a *legally enforceable ban on human reproductive cloning,* defining human reproductive cloning as placement in a uterus of a human blastocyst derived by nuclear transplantation. As you know, Congress has not chosen to separate the issues and provide for such a ban by itself.

From a scientific, medical, and medical ethical perspective, there was not considered to be a similar justification for a ban on nuclear transfer *(NT)* to produce human pluripotent stem cells. In order to judge the potential scientific and medical value of such research, we considered all experiments published in animal systems, and unanimously recommended that *biomedical research using nuclear transfer to produce stem cells be permitted,* and called for a broad national dialogue on the societal, religious, and ethical issues on this matter. I am here today to bring you up to date on these issues so that you can enlarge the debate on *societal* grounds.

Let me remind you of the process of producing such lines in mice, which presumably would be the blueprint for the production of human pluripotent cells. A somatic

cell (from skin, or other adult tissues) is placed into an enucleated egg, the cell resulting from that NT is stimulated to divide, resulting in an embryoid 'blastocyst'. That 'blastocyst' contains about 40 pluripotent (many potentialities) cells inside a hollow sphere of so-called trophoblastic cells. The trophoblast cells are necessary for the blastocyst to implant in the uterus, the trophoblast cells contributing to the placenta. The blastocyst cannot proceed to even the next stage of development unless it implants and receives signals and nutrition from the uterus. A blastocyst lacking the trophoblast cells cannot implant. The pluripotent cells of the preimplantation embryoid blastocyst can then be removed and cultured to produce the pluripotent stem cell line. These pluripotent cells lack the capacity to make reproductive clones, and only make all tissue types in a disorganized fashion. Neither these nor true embryonic stem cells can make embryos, or fetuses, and therefore it would be a misnomer to claim they can be used to generate' embryo farms'.

It has been shown in mice that the genome of the donor body cell is what is retained in the pluripotent stem cell line. Nuclei taken from mice with severe combined immunodeficiency (the so-called bubble boy disease) give rise to pluripotent stem cells that also have that disease, seen most graphically if the tissue HSC from these lines are transplanted into suitable radiated mice. The pluripotent cells can contribute to every other tissue, but can't make immune lymphocytes. Correction of the defective gene in the cell line corrects the disease even when transplanted into appropriate hosts. This suggests that one might be able to develop similar cell lines derived from humans with genetically determined diseases such as immunodeficiency, or adult or juvenile diabetes, or immune disorders such as lupus, rheumatoid arthritis, or multiple sclerosis, or neurodegenerative diseases like Lou Gehrig's, some Parkinson's, some Alzheimer's, Huntington's Disease, and all lysosmal storage diseases—just to name a few such diseases—to try to elucidate how certain genes lead to the disease, whether studied in test tubes or in immunodeficient mice. And this is only a short list of human genetically determined disorders.

There are now several experiments in mice that show at least some cancers can be used in NT to produce pluripotent cells, so not all of the mutations that lead to these cancers prohibit them from being reprogrammed to make pluripotent cells. At least one of these, malignant melanoma, has been shown by Rudi Jaenisch to redevelop melanomas if put into appropriate mice.

One could also begin to figure out how to develop tissue stem cells from a particular person that might be transplanted back into that person—perhaps after fixing the defective disease genes—a process called *therapeutic cloning* in the popular press. (This is the only NT application that is appropriately called therapeutic cloning). So you might think we would be encouraged at the potential medical advances in adult stem cell research, in embryonic stem cell research, and in NT stem cell research to expand our efforts for new discoveries and new therapies in these exciting areas. However, the bills put forward by Senator Brownback and Representative Weldon call for banning NT research, with criminal penalties at every stage of research as well as therapies derived from that research. *Before one enacts the first (that I know) ban on biomedical research in U.S. history based on ideology, not safety, we should realize what will be lost,* and think deeply about the political, medical, societal, commercial, and moral consequences of such a ban. To do so we need to know what experiments and therapies today, *cannot be accomplished with adult tissue stem cells or the allowed human embryonic stem cell lines.* These can be summarized in 4 areas:

(1) Genetic diversity of embryonic and pluripotent stem cell lines. The genetic diversity of the usable 9–64 lines currently available is that of the population that in the U.S. undergoes in vitro fertilization; they are largely white, well to do, and always infertile. There is no doubt that the wide variety of racial and ethnic populations that characterize America are not represented in these cell lines, and of course, it would be extremely unlikely if any had the genetically determined diseases such as sickle cell anemia, thalassemia, and adult onset diabetes, to name a few, prevalent in black, Mediterranean, and native American populations resident in the U.S. There are probably tens to hundreds of genetic disorders, and none will be represented in this limited number of cell lines. NT is a method to make sure they are represented.

(2) Genetically determined human diseases. The NT technology might give us cell lines important to understand how simple (one gene defect) or multigenic disorders are caused, and how they might be approached and treated. For example, Lou Gehrig's Disease (LGD) is multigenic, resulting in a loss of motor neurons with tragic consequences for reasons we don't understand. If one could have a pluripotent LGD cell line, one might be able to repair one gene

at a time, and determine if in test tubes, or in immunodeficient mice (systems wherein mouse embryonic stem cell-derived tissue stem cells can give rise to motor neurons and the muscle cells they serve)whether the disease development is halted. Knowing those genes as *validated targets* should be useful for medical scientists, gene therapists, stem cell transplanters, and even small molecule pharmaceutical companies.

(3) *Cancer cells.* All cancers differ from other cells in the body in that they have suffered several, if not many genetic mutations or alterations that play a role in their progress from a normal cell to a cancer cell that can spread and kill a person. There are, to date, no exceptions. It is therefore likely that NT research could make available pluripotent cell lines made from real patients' cancers capable of evolving the particular cancer, and these lines should be susceptible to the same kinds of research to define the dangerous genes, and how to attack them. For both reasons (2) and (3) shown above it should be clear that we are hoping for a chance to learn about how these terrible life-shortening diseases develop, how we can intervene, and eventually, how we might cure them. No other methods that I know of and that are presently available allow these kinds of approaches. It is hard for me as an MD and medical researcher to ignore such promising lines of inquiry.

(4) *Therapeutic cloning.* The possibility that we will someday be able to make NT stem cells from us for us could open the way for a broad scale development regenerative medicine. While it is undetermined whether these approaches will replace the few known adult tissue stem cell therapies, it would be foolish to bet the health of the American people that they will not; and in addition, there are many, many tissues that we do not have replacement stem or progenitor cells yet. And even the approved human embryonic stem cell lines will likely not be useful or allowed for direct transplantation therapies, as they are compatible with few or no persons, and they are all grown in a way that they could be contaminated with leukemia viruses from the mouse feeder layers they are grown on. At the same time one should not be susceptible to the hype that tomorrow, or even 5 years from now we will have transplantable cells from NT lines for therapies, as these cells are developed from early stage cells, and will need to undergo the changes all of our stem cells naturally undergo to give rise to mature tissue stem cells. We should remember that high quality research takes time, and we must not overestimate how quickly the work will go. But if we don't start, we'll never get there.

This last point deserves some comment. Congress has been wise enough to understand that the support of basic medical research eventually leads to medical breakthroughs and medical therapies. No line of fundamental biomedical research at the beginning results in short-term therapies. One hears often that embryonic stem cell research or pluripotent stem cell research must be lacking in possibilities as no cures have yet been found. Using that logic, funding NIH and NSF should be abandoned. Human embryonic stem cells were first reported in 1998, first distributed beyond the founder lab a couple of years later, and first allowed for NIH funding in 2002, following the President's executive order. Any clinical trial with cells takes at least 1–2 years to get the cells properly established to be safe and nontoxic, and of course several years of preclinical animal experiments to show there is an indication for a trial. It is frankly impossibly premature to conclude they will not work. And NT pluripotent stem cell lines have only been reported once, this year, in a preliminary report from South Korea.

Twice in the 20th century governments approached biomedical genetics research with the intent to regulate or ban it (albeit not criminalize it). In the late 1970s, and early 1980s the Cambridge Mass city council and the Berkeley CA city council considered prohibiting recombinant DNA research in their jurisdictions, and the issue of safety was raised in the U.S. Congress. Recombinant DNA is spliced together DNA segments, and the issue at that time was putting human genes like insulin into bacteria to produce human insulin for diabetics. Many thought such genetic manipulations could be dangerous, and others wished it banned because it offended them, or because they reserved to God the right to "create life". But instead of banning the research, the *NIH regulated* such research. Even today to carry out a recombinant DNA experiment with new methods or possibly dangerous genes it is required to seek and obtain approval from these regulatory bodies. What was the result? Only the birth of biotechnology, the expansion of these research techniques to every branch of biomedical research, and the annual saving or making better of >100,000 lives per year. Had this recombinant DNA research been banned those lives would be saddled with disease or lost. *The lost or impaired lives of those people would, in my view, be the moral responsibility of those who advocated or helped*

enact the ban. In addition biotech firms were started in the U.S., and U.S. citizens were first to get the treatment benefits, By now U.S. biotechnology companies rival classical Pharma companies for value and world leadership. The U.S. is the world leader in these advances, advances that were slow in coming, but undoubtedly have changed the lives of diseased patients for the better.

The second example occurred in the 1920s and 1930s in Russia. At that time Russia and the U.S. lead the world in genetics research. But in Russia a maverick geneticist named Trofim Lysenko became a science advisor to Joseph Stalin, and persuaded Stalin that Darwin and Mendel's views on natural selection were wrong. By Darwinism, for example, spontaneous variants could occur rarely, and might affect, for example, resistance to cold or dark in only about 1 in 1 million seeds. Another view, proposed by Lamarck, stated that gradual changes in light and temperature over the growing season would cause all plants to undergo adaptations, and that all germ cells would transfer such changes. In that view one could change the response to cold in a single plant, only requiring that winner adaptations would be inherited in seeds; such a result would have shaken up American genetics. Unfortunately for Russia Stalin chose Lysenko's proposed methods and potential results, a choice that proved to be wrong. The tried and true method of painstaking determination of the rare cold-resistant "mutants" and their selection for next generation's produce was left high and dry. So Lysenko was revered and Darwinists reviled. The Russian crops failed, and the next generation of Russian scientists were untrained in genetics. Several important Russian geneticists were blackballed and some jailed. Others, migrated to the U.S., or if already in the U.S., stayed, where they helped lead the U.S. to unquestioned leadership in the field. As a result for the next 50 years Russia produced no great geneticists and no great genetics. The biomedical revolution bypassed the Russians, as did medical treatments and the economic benefits that would have accrued.

I urge you to think hard whether you wish to overrule good science and medicine and ban some kinds of biomedical research and therapies for the first time in American history. In my own personal moral view, those in a position of advice or authority who participate in the banning or enforced delays of biomedical research that could lead to the saving of lives and the amelioration of suffering are directly and morally responsible for the lives made worse or lost due the ban, or even of a moratorium that would deny such treatments in that short window of time when it could help or save them. I recognize that for some there are strong religious and/or other moral bases for beliefs that the NT 'blastocyst' has the same rights as born friends and family. In our pluralistic society they have the sovereign right to act on their beliefs for their own conduct. But my reading of the oath I took upon receiving my MD that the health of the patients are my first priority. This supersedes any personal moral, political, ethnic, and religious beliefs that would block the treatment of current or future patients; and that oath has guided my career. If you have real concerns about our economy, or our ability to recruit and train the best and brightest for biomedicine, or our ability to develop and prescribe the best therapies for our patients, I believe you will choose the American way of sensible actions, and when appropriate, regulation, not abolition.

In summary, adult tissue stem cells, embryonic stem cells, and NT stem cells each have important and unique properties to allow the biomedical and clinical community the opportunity to pursue the understanding of human development, the regeneration of damaged tissues, the development of human genetic diseases, and the broadest possible approaches of translating those discoveries to the treatment of patients with grievous diseases. In my view it is irresponsible to fail to pursue all such avenues in parallel to stop or ameliorate the tragedies our families endure because of these diseases. And of course, in my view it is worse than irresponsible to ban these pursuits.

Thank you for your attention.

Senator BROWNBACK. Thank you, Dr. Weissman.

We will focus the hearing on adult stem cells, as I have stated that we were focusing on. We've had a series of hearings on many other types of stem cells where Dr. Weissman and others have testified at many times, and on cloning, so we want to focus on adult stem cell research, and that's the focus of the hearing.

Dr. Levesque, thank you very much for being here. Do you have some patients that you've treated, of Parkinson's? I believe on the next panel, one of your patients will testify, is that correct?

Dr. LEVESQUE. So far, we've transplanted one patient with his own neurons derived from his neural stem cells. We are to begin a phase two trial in the next few months with possibly an additional 15 patients.

Now, we've harvested many more patients to look at the presence of the adult neural stem cells in their brain, and this has been an ongoing effort for several years.

Senator BROWNBACK. Will you describe that one patient, I believe, that's going to testify next—Mr. Dennis Turner was your first patient, is that correct?

Dr. LEVESQUE. Yes, that's correct. Well——

Senator BROWNBACK. Describe his condition, if you would. And, actually, if Dennis could step up, that might help, if you don't mind doing that, Dr. Levesque.

Dr. LEVESQUE. Well, it's OK. I would have brought some videotape, you know, of medication before surgery and of medication after surgery. But Mr. Turner can speak for himself. Essentially, he had reached an advanced stage where he would have met criteria for implantation using any other type of cell therapy. As you know, previously the NIH funded a double-blind study using fetal tissue for Parkinson's disease. So using this same criteria, he would have been a candidate for this type of transplantation. But, instead, we used a population of cells derived from his biopsy of a cortex, which regenerated millions of his own neural stem cells.

Senator BROWNBACK. Will you break that down for me? Where did you get the stem cells from?

Dr. LEVESQUE. From his own brain.

Senator BROWNBACK. From his own brain. Where in the brain?

Dr. LEVESQUE. Nondominant prefrontal region.

Senator BROWNBACK. OK. And what did you do with the cells?

Dr. LEVESQUE. We placed these cells in the media—culture media in laboratory, and we isolated maybe 50 of these, what we call stem cells. And these cells began to divide for several months, until we had over 20 million of his neural stem cells. Then these cells were characterized. That is, we were able to prove that they can become neurons, glial cells, and other type of techniques to demonstrate they are stem cells. And then we induced these cells to mature prior to transplantation. And then he received an injection on one side of his brain. At that time, it was—the criteria was a unilateral implantation—at that time, he was extremely afflicted, and more severely on the right than on the left, so he received an implantation on the left hemisphere, which controls the right side.

Subsequent to this implantation, it took several months to see any significant improvement. In fact, it took over 6 months to see a benefit of this type of cell therapy. As you can imagine, we're dealing with a biological organ, which is the human body and the human brain, and this is not like a switch that you turn on and off to reverse the course of a disease or transform symptoms overnight. But, overall, the biological process took possibly 9 months to have a beneficial effect on his symptoms, and his symptoms then progressed and improved over the next 3 years, where his symptoms disappeared completely on the side that received implantation.

Senator BROWNBACK. Symptoms disappeared completely on the side that received it. So you're going to move this forward then to an additional scale of clinical trials?

Dr. LEVESQUE. Right. We need to study more patients. This is just one patient. We need to have a larger series of patients, and also evaluate the dosage to know exactly what the number of cells that needs to be transplanted to produce the most efficacious effect on the patient.

Senator BROWNBACK. Advanced Parkinson's disease, to the point of symptoms disappeared completely——

Dr. LEVESQUE. Right.

Senator BROWNBACK.—for this patient.

Dr. LEVESQUE. You have to realize that only one side was operated. The other side was left alone, and he has progressed significantly now on the opposite side. And, at this point, he'd like to be implanted on the opposite side, and this is something we will hopefully offer him in the near future.

Senator BROWNBACK. That's fantastic. And I'll look forward to his testimony.

Dr. Nelson, you've got a couple of patients from the gentleman that you've worked with in Portugal. They'll be here and testify. As this procedure has been developed—we'll hear from the two ladies—how has it been perfected? What else has been done to deal with these massive spinal cord injuries?

Dr. PEDUZZI-NELSON. I've tested a variety of things in the lab—different types of growth factors, pumping in growth factors, different types of matrices, different cell types, different types of stem cells and support cells—and all of them have, at one time or other, shown a small benefit. And what I've seen in the animal studies—and the reason why the animal studies are important is that when you're working with people, every injury is different; when you're working with animals, you can produce a large group of animals with the same type of injury, and then divide the animals up and give them different treatments, and have someone who's completely unaware of what treatment the animal received test these animals. And what we do is, we test them weekly over a course of a year and a half. And the surprising results were that the olfactory mucosa, as a source of adult stem cells, worked the best.

But there are also other cell types in the olfactory mucosa. There's a support cell called the olfactory ensheathing cell. And that cell, when it's purified by itself, others have found improvement just using that cell type.

So we think that olfactory mucosa definitely is something that's very promising. And if we can add some other combinations to this, we may see even further benefit. And there's a real lacking, in terms of rehab methods, that we need to perfect the rehab methods so we could see the maximum improvement in these patients.

Senator BROWNBACK. That's fantastic. I'll look forward to these witnesses testifying.

Senator Wyden?

Senator WYDEN. Thank you, Mr. Chairman.

Dr. Nelson and Dr. Levesque, I think you heard me go through the NIH website that outlines, in their view—the government's view—the limitations today on adult stem cell research. And I just

want to ask you if you share the views of the government, because it seems to me that you all are taking a very different approach.

For example, on the NIH website, it says, and I'll just quote here, "Adult stem cells are often present in only minute quantities, and can, therefore, be difficult to isolate and to purify." That's a pretty significant limitation——

Dr. LEVESQUE. That is correct.

Mr. HUTCHINSON.—that the Federal Government finds, and I'd be curious whether you two share the view of the National Institutes of Health on that point.

Dr. Levesque?

Dr. LEVESQUE. I agree. This is a difficult proposition, to isolate an adult neural stem cell. It's not easy. This is a known limitation of the adult stem cells. I mean, there a lot of unknown limitations from the embryonic stem cell point of view that cannot be understood because we don't have enough data or knowledge about this. So I think, as anything in science, we need to seek new aspect and new causation factors of disease, and we need to address the benefit, pros and cons, of all type of tools to treat the disorders.

So, yes, adult stem cells can be limited in their isolation. However, they have benefits, also, in the way that, with an autologous approach, you don't have to deal with the immune rejections of any implanted tissue. And——

Senator WYDEN. My time's going to be short, and I appreciate your saying you agree with the National Institutes of Health on that point. They also say that there's evidence that they don't have the same capacity to multiply as embryonic stem cells do. Dr. Nelson, is——

Dr. PEDUZZI-NELSON. Yes.

Senator WYDEN.—the NIH right, or what do you think?

Dr. PEDUZZI-NELSON. I would say that what—the paragraph you read probably represents some of the scientific view, but I think in the case of stem cells, less is more. OK? And the reason is, there's a problem with embryonic and fetal stem cells, is they grow too well. When you put them in animals, they grow too well and form tumors, and occasionally kill the animal. Adult stem cells exhibit a more controlled growth. They're not impossible to grow. I'm not the famous stem cell biologist here next to me, but, even in my own lab at the University of Alabama at Birmingham, they're fairly simple to grow, and they grow in a controlled manner, and it is possible to get enough stem cells to use as a treatment. And this controlled growth, I think, is the best option, because there is not these other problems, such as rejection.

Senator WYDEN. The government states that adult stem cells have more DNA abnormalities. Do you share that view or find it troubling?

Dr. PEDUZZI-NELSON. What I have found is that, using adult stem cells, we haven't found any abnormalities in the animals. And I think that statement—it takes me back to a story in my childhood where the neighbor said she would make—that Duncan Hines had developed a cake mix, and obviously they put a lot of research into it, and it has to be better than anything homemade. Well, I think that if you talk about abnormalities that develop in ourself, in the adult stem cells from our own body, and you're saying that

growing them in a very artificial culture situation leads to more abnormalities, I think at least some people would think that a better way to protect the stem cells is in your own body.

Senator WYDEN. Again, I think—you say some scientists share this view. This is the official position of the Federal Government, folks. Federal Government, on its website, is talking about the limitations on adult stem cell research that obviously you all don't see in the same way.

Let me ask you about an issue that I think goes to the heart, for me, of how we evaluate your views. You, in particular, Dr. Levesque, at page 3 of your testimony, are quite critical of embryonic stem cell research. It's in the third to last paragraph, talking about the ramifications of tumors and possible ramifications for the brain, and the like. My question to you is, have you done research involving embryonic stem cell lines so that you can make that comment on the basis of comparing research involving embryonic stem cells to adult stem cell——

Dr. LEVESQUE. I believe you refer to the paragraph where I state that the—there's a strong potential for the embryonic stem cells to generate any type of cells. The problems we have——

Senator WYDEN. My question, Doctor, is, have you done research involving embryonic stem cell research? That's a yes or no answer.

Dr. LEVESQUE. The answer is no.

Senator WYDEN. Thank you.

Dr. LEVESQUE. However——

Senator WYDEN. Dr. Nelson, have you?

Dr. PEDUZZI-NELSON. Yes, I have. I've done—used animal—there's no ban on animal research using embryonic or fetal stem cells, and I have. And I've also used adult stem cells that were similarly prepared. These experiments were done at slightly different times, but the results were very similar. They were slightly better with the adult stem cells. But if they're not done at the same time, you can't make a direct comparison.

Senator WYDEN. Let me ask you about the ethical concerns, Dr. Nelson, that you mentioned. You said you had ethical concerns with respect to this research, and that certainly is something that crops up again and again in this Committee. What exactly are your ethical concerns with respect to embryonic stem cell research? And, again, how are those concerns alleviated by looking to adult stem cell lines instead?

Dr. PEDUZZI-NELSON. I think there's no ethical controversy with regard to adult stem cells. I——

Senator WYDEN. I asked about yours.

Dr. PEDUZZI-NELSON. Oh.

Senator WYDEN. I'd like to know about your ethical concerns, as a scientist——

Dr. PEDUZZI-NELSON. OK.

Senator WYDEN.—with respect to embryonic stem cell research, so I can factor that in to your argument that the focus should be, by the government, on adult stem cells.

Dr. PEDUZZI-NELSON. I didn't present my ethical concerns. I do believe that, if given the option of a treatment, a direction of treatment, that has not led to tumors and death and overgrowth, and you have an option of a treatment, that all of the science that I've

looked at says that this is a better option for the treatment, and the fact that there are no ethical concerns using adult stem cells.

I am here, not on the basis of ethics or politics or anything else; I'm here because, in the last 12 years of my life, I have been obsessed with finding the best treatment for spinal cord injury. This has been my focus, and I haven't looked in either direction. And what I see out there is that there is a possibility that adult stem cell treatment might not go forward because it's a very difficult area to bring forward. It's difficult because, commercially, a lot of companies are less interested, at this point, in adult stem cells.

So my main reason for being here today has to do with trying to get the best treatment out there for spinal cord injury. Whether I'm pro-life or pro-choice, I wish that all these types of things could be kept out of the discussion, and we can just concentrate on the families and the patients and the people suffering out there.

Senator WYDEN. My time is up. And I would only say, ma'am, if we look to the patients and the families, they're making it clear they want Federal policy to change in this area. That's what my constituents come to town meetings and say, that's what public opinion polls say, that's what we hear again and again.

And I will only tell you that what I think is the reason that adult stem cell lines aren't being pursued by a lot of private companies is, I think that they agree with the National Institutes of Health. I mean, I thought it was very important, when we come to this hearing, as I think you have, to your credit, suggested, that we stick to the facts. And today, on the Federal Government's website, they outline at least four significant limitations with respect to using adult stem cell lines. And that's what's motivating the companies of this country. The reason the companies are hesitant to make investments in this area, not because any Member of the U.S. Senate wants to limit this research, the companies are reluctant to make the investments because they share the view of the National Institutes of Health that our research possibilities in this area are limited.

Dr. PEDUZZI-NELSON. I'd just like to mention——

Senator WYDEN. Mr. Chairman, I know my time is up, but I think——

Senator BROWNBACK. Just go ahead and—please go ahead and respond.

Dr. PEDUZZI-NELSON. Just one—two sentences. I'll make it two sentence. The procedure that I talked mainly about was the olfactory mucosa. It cannot be patented. OK? There is no patent. There is no way to get companies interested in there because there's no profit in there. That's why the struggle is for adult stem cells to go forward, is—if you have techniques that are a patent, you don't have intellectual property.

Senator WYDEN. Yes, I——

Dr. PEDUZZI-NELSON. And NIH doesn't tell researchers what direction to go, or they think this or think that. People go into their research labs and go forward with the best——

Senator WYDEN. I've made it clear that there are areas where clearly adult stem cell research can be useful. But what is even more clear is that the preponderance of scientific evidence is—and I think this is what is guiding these private companies looking to

investments—is that there are vastly more possibilities using embryonic stem cells.

Dr. PEDUZZI-NELSON. I think they might be interested in the money, too.

[Laughter.]

Senator BROWNBACK. Yes, I think that would be a fair point.

Senator Lautenberg?

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

Dr. Nelson, you brought up the subject, and I have to followup. And everybody is under oath automatically when you're testifying before a Committee, even if the hand isn't raised and you don't take it. Do you—are you a member of a pro-life group in any way?

Senator BROWNBACK. Is that a relevant——

Senator LAUTENBERG. Yes, it's——

Senator BROWNBACK.—question——

Senator LAUTENBERG.—relevant to me, Mr. Chairman. And I do have my right——

Senator BROWNBACK.—for an adult stem cell hearing?

Senator LAUTENBERG.—as a Member of the Committee, to ask the questions. And I can't—you can't give me a stacked deck unless I know what the cards are. And you'll forgive me, Mr. Chairman.

Senator BROWNBACK. Well, but I really——

Senator LAUTENBERG. Mr. Chairman——

Senator BROWNBACK. Is that a relevant question?

Senator LAUTENBERG.—I want you to look at the testimony, if I must, when it talks about, "I, Ronald Reagan," and she quotes the President of the United States, and then denies any ethical connection to this. And I want to challenge this, and I want to find out the truth, if I may, Mr. Chairman, pursue the course of——

Senator BROWNBACK. Then I guess we should have Dr. Weissman, too, say that?

Senator LAUTENBERG. Sure. I'd ask—you can ask it on your time, Mr. Chairman.

[Laughter.]

Senator BROWNBACK. If the witness chooses to answer.

Senator LAUTENBERG. Well, if the witness doesn't choose to answer, then it can be contempt.

And are you a member?

Senator BROWNBACK. No, it cannot.

Senator LAUTENBERG. Mr. Chairman, there's an obligation to answer the question that's put to you when you sit in the witness chair. Why are we having this—why are we having this debate? All I—let me defer and give you a chance to think about it.

Dr. Levesque——

Dr. Levesque: Yes?

Senator LAUTENBERG.—does a single case of an outstanding reaction to a process make a scientific enterprise a valid one to say that that's the way we ought to go?

Dr. LEVESQUE. Well, it's just one step. I mean, we need to evaluate, as I said, more studies.

Senator LAUTENBERG. So that single case that you talked about is not really indicative of a sense of an appropriate scientific course of study.

Dr. LEVESQUE. Well, I'd disagree with that. I think science has to further the evaluation of——

Senator LAUTENBERG. Right.

Dr. LEVESQUE.—this therapy, or not. Science is built on several steps, and this is just one step——

Senator LAUTENBERG. Just one step, all right. Thank you.

Dr. Nelson, are you now a member of a pro-life committee in any way?

Dr. PEDUZZI-NELSON. In an attempt to not be in contempt of court, I honestly say I don't remember joining any of the groups that—you know, that are——

Senator LAUTENBERG. OK, but you are concerned about the ethics of science, because——

Dr. PEDUZZI-NELSON. I think a lot of Americans do not believe in creating life to destroy it. You know, I——

Senator LAUTENBERG. Yes, OK.

Dr. PEDUZZI-NELSON.—think that's a concern——

Senator LAUTENBERG. Fine. That——

Dr. PEDUZZI-NELSON.—of some Americans.

Senator LAUTENBERG.—that summarizes an attitude, that you are more concerned about the ethic, in my view, because you hear, quote, the revered President Ronald Reagan, "By virtue of the authority"—you quote him—"vested in me by the Constitution and laws of the United States do hereby proclaim and declare the unalienable personhood of every American from the moment of conception til natural death." So you use that as a reference. So that, then, tells me that that's where your studies are focused, that you're hewing to a line of morality, as you see it, that governs your scientific behavior. Is that a fair statement?

Dr. PEDUZZI-NELSON. I'd say I included that in my testimony because——

Senator LAUTENBERG. Yes.

Dr. PEDUZZI-NELSON.—there are people out there who respected—very much respected Ronald Reagan as a President, and——

Senator LAUTENBERG. As a scientist?

Dr. PEDUZZI-NELSON. They respected him—no, I'm saying that, in the U.S., that many people respected President Reagan, and recently the reason why there is so much attention right now to this area is because of the suggestion that this might have helped President Reagan or that——

Senator LAUTENBERG. No, but didn't Mrs. Reagan say that she would hope that we'd pursue stem cell—embryonic stem cell research?

Dr. PEDUZZI-NELSON. I'm just—I presented that as a statement. I didn't make this up. I think——

Senator LAUTENBERG. No, I know. But——

Dr. PEDUZZI-NELSON.—this is a——

Senator LAUTENBERG. But this——

Dr. PEDUZZI-NELSON.—correct quote that—you know, if we wanted to——

Senator LAUTENBERG. If you'll forgive me——

Dr. PEDUZZI-NELSON.—honor someone's memory——

Senator LAUTENBERG. It became—yes, it became, however, an anchor for your testimony on science. And, therefore, it has to have some relevance, or you wouldn't have put it in there. And I just wonder whether we're now going through a political discussion or a scientific discussion.

Dr. Weissman, as a researcher who works mainly with adult stem cells, do you support the Federal funding of embryonic stem cell research?

Dr. WEISSMAN. Oh, of course. But I don't think it goes far enough. So I support what's happened. I think it was a brave move forward to at least make those 64 or so cell lines available for study and government funding. But now, on reflection, I think it just doesn't go far enough.

Could I clarify one very small point——

Senator LAUTENBERG. Please do.

Dr. WEISSMAN.—just so everybody understands? Embryonic stem cells, mouse or human, can cause tumors if put in the body while they're still just embryonic stem cells. But once you generate a mature tissue cell, they do not cause tumors. That's scientifically accurate.

Senator LAUTENBERG. Thank you very much.

Because in Dr. Nelson's testimony it says, "the oft-stated advantage that embryonic stem cells can make every cell in the body is not an advantage for people with disease or injuries," is that a statement that can reliably be made, Dr. Weissman?

Dr. WEISSMAN. Well, not in my view. And I think I've made the point that what we need to do to be able to understand each of these various diseases is not just think of the cells that you get out as therapies, but as tools or engines of discovering what caused that disease. That's where we really need to be able to move to move this field forward for the long term. So I disagree with that point of view.

Senator LAUTENBERG. Thank you very much.

Senator BROWNBACK. Senator Nelson?

Senator NELSON. Thank you, Mr. Chairman.

Senator BROWNBACK. Thank you.

Senator NELSON. Dr. Weissman, I'm quoting from—let's see, this is your article in the *New England Journal of Medicine,* "I believe that new lines of human embryonic stem cells will be needed." And then you go on to say, "One way is by transferring somatic cell nuclei into enucleated eggs, nuclear transplantation." Would you describe that procedure?

Dr. WEISSMAN. Sure. And this has been done successfully many times in mice, maybe once or two times in humans. So you take the nucleus from a body cell, let's say a skin cell. That cell has genetically been programmed, at that point, to be a skin cell, and has the genes on to be skin, but not the genes on to be early pluripotent cells. When you put that into an egg, by injection, that had its own genetic material removed, what's left in the egg, remarkably, stimulates the nucleus of that skin cell to reprogram itself, to shut down skin cell genes, to open up genes that would make it very early stage.

Then you have to do something to make it divide. Normally, when a sperm/egg fuse, there's no question, because what's stimu-

lates division. But you stimulate it to divide. And after, if you're lucky—and this is rare—after about seven or eight or nine cell divisions, you have a ball of cells, the outside of which could, if implanted, start to form a placenta, and the inner cells are these pluripotent cells, the ones from which you make a cell line. It has no nerve cells, it has no hard cells, it has no determined cells at all.

Senator NELSON. So you're taking the nucleus out of a cell, you're transplanting a nucleus in that you want to multiply.

Dr. WEISSMAN. Right.

Senator NELSON. And so you're not dealing from a fertilized egg.

Dr. WEISSMAN. That's right.

Senator NELSON. You're taking the nucleus out.

Dr. WEISSMAN. At no point do you have fertilization occurring in the natural way of making an embryo or a fetus.

Senator NELSON. Is there progress between adult stem cells and the embryonic stem cells?

Dr. WEISSMAN. There is tremendous progress going on in both fields. I hope you understand that my own chosen field, and my own consulting with industry, is all on adult stem cells. I believe in them deeply. The kinds of experiments that we've done with blood-forming stem cells, we've already treated 70 to 80 patients, I think successfully, in clinical trials. So I believe in it. But what we want, what we need, out of nuclear transfer to produce these pluripotent stem cell lines is entirely different. We cannot possibly do that with adult stem cells. We cannot possibly do that with the approved lines from in vitro fertilization clinics. In vitro fertilization clinics, we must admit, attract people in the United States who are mainly white, middle-class to well-to-do, always infertile. There are no diseased cell lines coming out of an in vitro fertilization clinic, so we can't learn about the diseases that we promised the American people we want the help do. The whole reason for a National Institutes for Health—H for Health—is that we would commit ourselves to carry out research on all diseases, that we wouldn't look for barriers in the way not to do it.

Senator NELSON. Dr. Nelson, in the procedure that Dr. Weissman has just described, transferring somatic cell nuclei into enucleated eggs, nuclear transplantation, do you have an ethical problem with that procedure?

Dr. PEDUZZI-NELSON. I think one of the things we have to remember—I'd just like to clarify that this is the same procedure that was used to produce Dolly, the sheep, which is a real sheep. The problem I have with this procedure is that I see that millions of dollars can be made from these patent-able cell lines. And right now, you could get adult stem cells from people with these various diseases, or a strong genetic background to develop these various diseases. You could get these cells, and not have one cell line from one patient that has, for example, juvenile diabetes, but get a large number of stem cells in culture so that they can be evaluated. So I think this is a better research direction.

Again, the problem is, the biotech industry expects that these patents on these cloned stem cell lines are going to be worth millions of dollars when you patent these. If you just got an adult stem cell from a child or an adult, and got it from a wide variety

of people that either have the disease or have a strong likelihood of getting the disease, I think this is a much better research direction.

Senator NELSON. You certainly answered that that's your preference in the research direction. The question was, Do you see an ethical problem with nuclear transplantation?

Dr. PEDUZZI-NELSON. The ethical problem that I see is that I don't believe that it's—that you should create human life just to destroy it for some vague scientific purpose. I think that there is a better research direction that the people out there, the patients, deserve to have pursued. It's a less profitable direction. And because it's less profitable, I don't think it is going to be pursued.

Senator NELSON. What was the verb or the adjective that you used—did you say "destroy" human life? What was the verb you used?

Dr. PEDUZZI-NELSON. I'm sorry, I guess I have problems with verbs here. I don't remember my exact statement. In this process, you would create a cell that, if it was implanted in the uterus, could develop into a person. And so, I do consider this human life.

Senator NELSON. Even though that cell was set to be discarded.

Dr. PEDUZZI-NELSON. It would be lots of cells that would be set to be discarded. But if you did take that cell—and we're calling it somatic nuclear transplantation—transplant, rather than cloning—that cell, if you put it into the uterus, could develop into a human being.

Senator NELSON. And so—I'm trying to understand your reasoning—so the fact that that cell could develop into a human being is your objection to using nuclear transplantation for the purpose of research.

Dr. PEDUZZI-NELSON. My objection to it is, one, I think there are better options that—one, there are better options that will make less money, that will never be pursued; and, two, I do consider it needless destruction of human life.

Senator NELSON. OK, that's what I was trying to get at——

Senator BROWNBACK. Your time is——

Senator NELSON.—to get your——

Senator BROWNBACK.—up, Senator Nelson. We need to head on. Do you have one quick one so we can get the next panel up?

Senator NELSON. I'm legitimately trying to understand this issue, Mr. Chairman, as to why this gets to be such a cat fight over ethics when we've got such tremendous promise for research and advancing toward the cure of diseases. So I'll continue my questioning later.

Senator BROWNBACK. Thank you.

Senator WYDEN. Mr. Chairman?

Senator BROWNBACK. Yes?

Senator WYDEN. Mr. Chairman, thank you. Just one quick one. And this goes to—again, to the NIH website, Dr. Weissman.

[Laughter.]

Senator WYDEN. The government says that adult stem cells don't give rise to a lot of the tissue types that would be important to people. My question to you is—embryonic stem cells can be used to grow a variety of tissues. Are adult stem cell lines more limited?

Dr. WEISSMAN. Yes.

Senator WYDEN. So——

Dr. WEISSMAN. And this, we've tested directly. I work with both mouse embryonic stem cells and mouse and human hematopoietic, blood-forming, and neural. So the neural stem cells only make brain cells. They do it beautifully, they grow well. Michel was absolutely right, they are something we want to test and we hope will work very well.

The embryonic stem cells, being pluripotent, can give rise to every tissue in the body. We don't yet have adult stem cells for every tissue of the body.

Senator WYDEN. Mr. Chairman, thank you.

Senator BROWNBACK. Thank you.

We'll have our—I want to thank this panel of witnesses. I think they've been quite illuminating, and this science has developed significantly, and I appreciate all of your testimony, even if it can be difficult to do. Thank you very much for being here. And, more importantly, thank you for your work. That's extremely important.

Now I have a panel of patients that'll be coming forward. Ms. Laura Dominguez, from San Antonio, Texas; Ms. Susan Fajt, from Austin, Texas—both had massive spinal cord injuries and will now be here to testify; Mr. Dennis Turner, we've heard spoken of already, was a Parkinson's patient, has had treatment—are the three patients that we will have on this panel. And then Dr. Robert Goldstein, from the Juvenile Diabetes Research Foundation in New York, will also testify.

[Pause.]

Senator BROWNBACK. I'm excited to hear from this panel, and I want to encourage all of you to be calm; nothing to be nervous about. I know several of you—OK, that's easy for me to say, I apologize. But I do hope you can be calm and just enjoy this, because I really think you're an inspiration to a number of people that are struggling with horrific difficulties. You represent the tip of the spear, going forward.

Congressman Gonzalez, I understand one of the witnesses is a constituent of yours that you would like to introduce. And then, once we do that, I would like to go, immediately to a video of Laura Dominguez and Susan Fajt. It's a short video, showing some of their progress, if that would be acceptable.

Congressman?

STATEMENT OF HON. CHARLES A. GONZALEZ, U.S. REPRESENTATIVE FROM TEXAS

Mr. GONZALEZ. Thank you.

Mr. Chairman, Members of the Committee, thank you very much for giving me this opportunity. Of course, I represent the area from which both, of course, Laura and the Dominguez family would—actually reside. I have known her father for a number of years, having been a state district judge, and we used to refer to in those days as a "baby lawyer," he used to appear before my court.

I do want to preface my own statement, and it's going to be very short, but that it had been some years since I had seen Laura, and the truth is, it had been maybe 6 years. I guess she was about 12 or 13 years of age. And, at that time, I saw her at a wonderful dance, a celebration that we have in San Antonio. And she had the

most beautiful dress on. And I remember, she may have been a member of someone's court, which they have this big celebration. But she was not only walking, but she was dancing. And so I would hope that we all join forces and hands and open every possible door to research that is out there so that one day again I can go to another dance, see the Dominguez family, and see Laura dance.

I am very honored to introduce to this distinguished Committee, Laura Dominguez. Laura is a smart and fun-loving 19-year-old. She enjoys traveling and, just like many other teenagers today, spending time on her computer.

Laura is also one of 200,000 Americans living with a spinal cord injury. At the age of 16, Laura was in a car accident that caused her neck to break. Doctors said she would never walk again. This young woman was undaunted by the prognosis, and has since exhibited amazing courage to prove these doctors wrong.

Laura is here today to put a face with the often abstract debates in which we policymakers often engage. She is an example of the miraculous strides that can be made in overcoming severe spinal cord injuries, if only we concentrated more resources to such goals, despite our differences on approach.

Again, it's with great honor, as her representative and a friend of the Dominguez family, to introduce to this Committee, Laura Dominguez. And thank you very much.

Senator BROWNBACK. Thank you, Congressman, and that is a beautiful image—a dance, and to see that happen again.

We have a short video showing some of the start and a point where we are now for both Laura Dominguez and Susan Fajt. And if you'd turn that video on, please.

Ladies, if either of you want to describe the status of where you are in these, please speak up.

Ms. FAJT. That would be myself, Susan Fajt. I am swimming in Texas at Joy Braun's house, one of my dear friends. And I'm also speaking, at the present time, about my quest for the cure.

Senator BROWNBACK. I don't know if we have sound with that video.

[Video presentation.]

Senator BROWNBACK. So this is a PBS special. That is one big smile, Laura. Wait til you see her dance.

Laura Dominguez, you're welcome to testify, and I'm pleased—we are honored to have you here.

STATEMENT OF LAURA DOMINGUEZ

Ms. DOMINGUEZ. All right, thanks.

Okay, so 3 years ago, while on my way home from summer school, my brother and I were involved in a car accident that left me paralyzed from the neck down. The accident was caused by an oil spill on the highway, an oil spill that we had nothing to do with, but, by chance, was on the road in our lane. I suffered a C6 vertebrae burst, and my spinal cord was severely damaged. In addition to the C6 burst, I also had a C1 and C4 fracture. So I came close to being gone.

Anyways, at the time, the doctors gave me absolutely no chance of ever walking again. I refused to accept their prognosis, and began searching for other options.

After being hospitalized in several hospitals for almost 1 year, my mother and I relocated to San Diego, California, so that I could undergo extensive physical therapy. While in California, we met a family whose daughter was also suffering from a similar spinal cord injury. They were also looking for other alternatives to deal with spinal cord injuries.

After extensive research and consultations with medical experts in the medical field of spinal cord injuries, we also—we all decided the best procedure that exists today was being performed in Portugal. We teamed up with the Nader family, which was the family from San Diego, and also a group of doctors from the Detroit Medical Center, and flew to Portugal to undergo this new surgical procedure.

The surgery involved the removal of tissue from my olfactory mucosa, and transplanting it into my spinal cord at the injury site. Those procedures—the harvesting of the tissue and the transplant—were done at the same time. I was the tenth person in the world, and the second American, to have this procedure done.

After the surgery, I returned to California to continue physical therapy. I stayed there until July 2003, and then returned back home. At that time, an MRI was taken, and it revealed that my spinal cord had begun to heal. Approximately 70 percent of the lesion now looked like normal spinal cord tissue. I was also starting to regain feeling in my upper body, and, within 6 months, I had regained feeling down to my abdomen.

Improvements in my sensory have continued until the present time. I can now feel down to my hip level, and have started to regain feeling and some movement down to my legs. My upper body has gained more strength and balance.

Another one of the most evident improvements has been my ability to stand, and remain standing, using a walker, with minimal assistance. When I stand, I can contract my quadriceps and hamstring muscles. I can also stand on my toes when I am on my feet. And, more importantly—oh, when laying down in a prone position, I am able to move my feet.

My training has continued to this day, and I am able to better use the muscles in my hips. I am able, with assistance, to walk, with braces, a distance of 114 feet. It takes approximately 30 minutes to walk this distance, and it is extremely tiring, but it can be done.

I will continue to challenge myself until I can fully walk again with little or no assistance from braces or the help of a physical therapist. I know this will be possible by my 21st birthday.

It is my understanding that the nervous system is one of the most difficult and complex to repair after an injury or trauma, but, in my case, the procedure that was performed in Portugal is working, as I have regained more feeling and movement. Some of the movements that I am able to do is a function that is controlled by the very tip of the spinal cord. Although the intensive physical training that I have has enhanced my ability to regain strength and movement, I did not have the type of function and feeling I have now prior to the surgery.

It only stands to reason that if stem cells can repair the complex functions of the spinal cord, they can be used to repair other in-

jured internal organs or other body parts, whether an injury is caused by trauma or disease. The way I see it, scientists have been given the knowledge and tools to develop and make use of adult stem cells. This knowledge should be taken full advantage of to help people overcome injuries or terminal illness. At the very least, people can benefit from the possibility of a better quality of life.

My life changed from one minute to the next. A catastrophic injury can happen to any person under any circumstance, whether it be a car accident or some other innocent event or occurrence. The U.S. has been the world leader in science and health, and its citizens should not be forced to go to other countries to look for help or cures. The tools to help Americans should be made available in this country.

Thanks.

[The prepared statement of Ms. Dominguez follows:]

PREPARED STATEMENT OF LAURA DOMINGUEZ

My name is Laura Dominguez. I am 19 years old and live in San Antonio, TX. Three years ago, while on the way home from summer school, my brother and I were involved in a car accident that left me paralyzed from the neck down. The accident was caused by an oil spill on the highway. An oil spill that we had nothing to do with, but by chance was on the roadway in our lane. I suffered a C6 vertebrae burst fracture and my spinal cord was severely damaged. At that time doctors gave me absolutely no chance of ever walking again. I refused to accept their prognosis and began searching for other options.

After being hospitalized (in several hospitals) for almost a year, my mother and I relocated to San Diego, CA so that I could undergo extensive physical therapy. While in California, we met a family whose daughter was suffering from a similar spinal cord injury. They were also looking for other alternatives to deal with spinal cord injuries. After extensive research and consultations with medical experts in the field of spinal cord injuries, we decided the best procedure, that exists today, was being performed in Portugal. We teamed up with the Nader family, a group of Doctors from the Detroit Medical Center, and flew to Portugal to undergo this new surgical procedure.

The surgery involved the removal of tissue from my olfactory sinus area and transplanting it into my spinal cord at the injury site. Both procedures, the harvesting of the tissue and the transplant were done at the same time. I was the tenth person in the world and the second American to have this procedure done.

After the surgery, I returned to California to continue physical therapy. I stayed there until July of 2003 and then returned back to San Antonio, TX. At that time an MRI was taken and it revealed my spinal cord had begun to heal. Approximately 70 percent of the lesion now looked like normal spinal cord tissue.

I was also starting to regain feeling in my upper body and within six months I had regained feeling down to my abdomen. Improvements in my sensory feelings have continued until the present time. I can now feel down to my hip level and have started to regain feeling and some movement down to my legs. My upper body has gained more strength and balance. Another one of the most evident improvements has been my ability to stand and remain standing, using a walker, and with minimal assistance. When I stand I can contract my quadriceps and hamstring muscles. I can also stand on my toes when I am on my feet. And more importantly, while lying down in a prone position, I am able to move my feet.

My training has continued to this day and I am able to better use the muscles in my hip area. I am able, with assistance and the use of braces, to walk a distance of over 1,400 feet. It takes approximately thirty minutes to walk this distance and it is extremely tiring, but it can be done. I will continue to challenge myself until I can fully walk again with little or no assistance from braces or the help of a therapist. I hope . . . no, I know . . . this will be possible by my 21st birthday.

It is my understanding that the nervous system is one of the most difficult and complex to repair after an injury or trauma. But in my case, the procedure that was performed in Portugal is working as I have regained more feeling and movement. Some of the movements that I am able to make are functions that are controlled by the very tip of my spinal cord. Although the intensive physical training that I

had enhanced my ability to regain strength and movement, prior to surgery I did not have the type of function and feeling that I have now.

It only stands to reason that if adult stem cells can repair the complex functions of the spinal cord, they can repair and help other injured internal organs or other parts of the body, whether an injury is caused by trauma or disease. The way I see it, scientists have been given the knowledge and tools to develop and make use of adult stem cells, whether they are derived from tissue removed from the olfactory mucosa or otherwise. This knowledge should be taken full advantage of to help people overcome injuries that can be helped by stem cells or people that suffer from some terminal or debilitating diseases. At the very least, some people can benefit from the possibility of a better quality of life.

My life changed from one minute to the next. A catastrophic injury can happen to any person under any circumstance, whether it be a car accident such as mine or some other innocent event or occurrence. The U.S. has been the world leader in science and health and its citizens should not be forced to go to other countries to look for help or cures. The tools to help Americans should be made available in this country.

Senator BROWNBACK. Thank you. Wow, that's beautiful.

Susan Fajt, which—I love that last name.

Ms. FAJT. Thank you, Senator.

Senator BROWNBACK. Let's hear your testimony.

STATEMENT OF SUSAN R. FAJT, SPINAL CORD INJURED RECIPIENT OF OLFACTORY MUCOSA TRANSPLANTATION

Ms. FAJT. Please bear with me, mine is much longer than Laura's.

OK. Hello, my name is Susan Fajt, and I would like to thank Chairman Brownback and Members of this Committee for this opportunity to tell you of adult stem cell treatment I received for spinal cord injury in Portugal, by Carlos Lima, and its results to date. But, first, allow me to share with you some basic facts about spinal cord injury to explain why I chose Dr. Lima's procedure.

On November 17, 2001, I suffered a spinal cord and became paralyzed in an auto accident. My life is changed in ways unfathomable. Emotions run strong, and decisions must be made to end needless suffering. I chose to live and fight for a cure. Perhaps paralysis has robbed me of my freedom, but it can never take away my belief that a cure is attainable through research. There are currently no effective treatments available for spinal cord injury in the United States.

When I was injured, I was 24 years of age, and I loved life more than you can imagine. Today, I have been given a great honor to tell you the story of my quest for a cure for this catastrophic condition.

Once realizing that my injury was no longer a nightmare, but a devastating reality, I set out to find the best possible treatment in hopes I would be cured and recover everything in which I had lost. After tears of pain and years of searching, I found, through my own research, Dr. Carlos Lima in Portugal. My treatment with Dr. Lima took place on June 17, 2003. I was the eleventh patient in the world, and the third in the United States, to receive this treatment.

Dr. Lima used adult stem cell treatment that uses an olfactory mucosa graft to promote axons to bridge the site of contusion, in hopes that my functional recovery would help me to once again walk, run, dance, and do everything I love, not to mention normal

daily activities which are so easily taken for granted, such as bowel and bladder control.

Only part of my dreams have been attained, but I've come farther than any of my American doctors have ever thought. My most recent MRI took place 5 days ago. The doctors were in disbelief at the improvement they saw where my spinal cord had been injured.

I have recovered some functional improvement through Dr. Lima's procedure, such as the ability to hold my bladder and, at times, even void on my own. Sensation has been restored, though it is not completely normal. When concentrating, I am now able to contract my thighs; once again, this was also impossible before my surgery in Portugal. But, most important on my way to recovery, is that I can now walk with the aid of braces. I am now preparing to shed the shell of this wheelchair, which has confined me for over 2 years, to more often use my braces and walker for mobility purposes. This is something my doctors here in American told me would never be possible with my level of injury, and to accept my fate. With Dr. Lima's adult stem cell-based therapy, I have accomplished much more than the U.S. doctors said was possible, but this is only the first step to a complete cure.

The next step is to find a combinational treatment, as well as an excellent rehabilitation program that will complement the results of Dr. Lima's surgery so that a complete recovery can be obtained from a spinal cord injury. I have literally gone all over the world in a quest for a program that will allow me to benefit as much as possible. Unfortunately, no program exists as of to date.

Through love and faith, my father and I have taken upon an endeavor of creating new devices that assist me in working out 2 to 3 hours each day to reach my maximum potential. In the near future, I hope to open a rehabilitation program so that others can benefit from our innovative equipment.

Spinal cord injury is one of the cruelest injuries to affect the human condition. It causes extreme neurological pain and excruciating psychological trauma, amongst other things. Fortunately, I am not built to accept failure, so I plead with you to hear my cry for funding and other support for therapies, such as the one I received, that will free me and millions of others who also suffer in this primitive wheelchair.

A cure for spinal cord injury will not be an easy task; however, when there is a will, there is a way. In addition to increasing funding to record levels, increasing public awareness about spinal cord injury and about treatments such as Dr. Lima's which are showing real results is imperative and desperately needed.

The U.S. taxpayers pay over 30 million per day on care for spinal cord injury, and only 68 million per year in a search for a cure. Common sense tells me that by taking away 2 days of our care and, in its place, using this money for a cure, time will inevitably be on our side.

Medical research in the U.S. is more advanced and far superior to any other country in this world, yet citizens such as myself risk their lives and are forced to seek treatment from foreign countries.

Researchers need to be held accountable by the U.S. Government to design and implement research that results in human clinical trials. No more research for the sake of research. Furthermore,

funding needs to be invested in staggering amounts for rehabilitation programs, as we have nothing of substance to help us recover after sustaining a spinal cord injury.

I ask you for just one moment to imagine if I were your daughter, wife, or loved one. Would you help me in my quest, and take the opportunity you have before you to promote and publicize this research, which has already helped me, so that 1 day I may dance the dance of life again, or would you allow me to suffer needlessly? The matter of funding medical research is of great importance, and I plead with you to do what your heart tells you. Please redirect the research in this country so that no—more resources and public awareness are given to treatments such as the one I received in Portugal. Free us from paralysis, and, in return, at the end of your life, you will know you have left this world a better place than what you have found it.

In closing, I will echo the words that the Honorable President Ronald Reagan spoke to Gorbachev, "If you seek peace, tear down these walls." Members of the Committee, if you seek cures for the millions of Americans currently suffering from spinal cord injuries and diseases, tear down these walls and free us from our wheelchairs.

Thank you, and godspeed.

[The prepared statement of Ms. Fajt follows:]

PREPARED STATEMENT OF SUSAN R. FAJT, SPINAL CORD INJURED RECIPIENT OF OLFACTORY MUCOSA TRANSPLANTATION

Thank you Chairman Brownback and members of Committee, for this opportunity to tell you of the treatment I received for spinal cord injury in Portugal and its results to date. But first, allow me to share with you some basic facts about spinal cord injury to explain why I chose Dr. Lima's procedure.

On November 17, 2001, I suffered a spinal cord injury and became paralyzed in an auto accident. My life has changed in ways unfathomable. Emotions run strong and decisions must be made to end needless suffering. I chose to live and fight for a cure. Perhaps paralysis has robbed me of my freedom, but, it can never take away my belief that a cure is attainable through research. There are currently no treatments available for spinal cord injury in the U.S.

When I was injured I was twenty four years old, I loved life more than you can imagine! Today, I have been given a great honor to tell you the story of my quest for a cure for this catastrophic condition. Once realizing that my injury was no longer a nightmare but devastating reality, I set out to find the best possible treatment in hopes I would be cured, and recover everything in which I had lost.

After tears of pain and years of searching, I found Dr. Carlos Lima in Portugal. He used a Olfactory Muscosa graft to promote axons to bridge the site of contusion in my hopes that functional recovery would help me to once again walk, run, dance, and do everything I would love not to mention—normal daily activities which are so easily taken for granted, such as, bowel and bladder control.

Sadly, only part of my dreams has been attained. I have recovered some functional improvement through Dr. Lima's procedure such as, the ability to hold my bladder and at times even void on my own. Sensation has been restored, though it is not completely normal. When concentrating I am now able to contract my thighs, once again this was also impossible before my surgery in Portugal. I can now walk with the aid of braces, which my doctors here in America told me would never be possible with my level of injury and to accept my fate. With Dr. Lima's surgery, I have accomplished much more than my U.S. doctors said was possible but this is only the first step to a complete cure. The next step is to find combination treatments as well as an excellent rehabilitation program that will complement the results of Dr. Lima's surgery so that a complete recovery can be obtained from a spinal cord injury. I have literally gone all over the world in the quest for a program that will allow me to benefit as much as possible. Unfortunately, no such program exists to date. Through love and faith, my father and I have taken upon an endeavor of creating new devices that assist me in working out to my maximum potential.

In the near future, I hope to open a rehabilitation program so that others can benefit from our innovative equipment. Spinal cord injury is one of the cruelest injuries to affect the human condition, most occur to young people who are just beginning to embrace their lives as adults. It is an injury that destroys the human body, causes extreme neurological pain, and extreme psychological trauma.

Fortunately, I am not built to accept failure, so I plead with you to hear my cry for funding for research that will me and millions of others who also suffer from this primitive wheelchair.

A cure for spinal cord injury will not be an easy task. However, when there is a will there is a way! Increasing funding to record levels that is specifically directed at injuries and diseases is imperative and desperately needed.

The U.S. taxpayer pays over 30 million dollars per day on care for spinal cord injury and only 68 million per year in a search for a cure. Common sense tells me that by taking away two days of our care and in its place use this money for a cure, time will inevitably be on our side.

Medical research in the United States is more advanced and far more superior to any other country in the world. Yet citizens, such as myself, risk their lives and are forced to seek treatment in foreign countries because treatments are not available in the U.S. Researchers need to be held accountable by the U.S. government to design and implement research that results in human clinical trials. Furthermore, more research dollars need to be invested in clinical trials and rehabilitation. I ask you for just one moment to imagine if I where your daughter, wife or loved one. Would you help me with my quest and take the opportunity you have to fund research so that I may one day dance the dance of life again, or would you allow me to suffer needlessly?

The matter of funding medical research is before you and I plead with you to do what your heart tells you. Please re-direct the research in this country so more money is directed at curing injuries and diseases instead of the majority of the money going to basic research that is centuries away from applied applications. In this way, people do not have to go to other countries for treatments. Free us so that at the end of your life you will know you have left this world a better place than what you have found it.

In closing, I will echo the words that the Honorable President Ronald Regan spoke to Gorbachev, "if you seek peace. . .tear down this wall!" Members of the Committee, if you seek cures for the millions of Americans currently suffering from spinal cord injuries and diseases, tear down these walls and free us from our wheelchairs!

Thank you.

Senator BROWNBACK. Thank you, Susan.

With the indulgence of Senator Wyden, could—are either of you willing to demonstrate and physically say, "Here's where I was, and here's what I can do now," and show us? Or, I don't want to put you on the spot and in a nervous position, if you're not—but if you are, we would obviously appreciate that.

Ms. FAJT. Well, last time I came, I was prepared to walk, and I brought my braces, and I did do that in front of one of the other Senators. And this time, being that I decided to focus more on the mental, instead of the physical. Otherwise, I would have brought my braces, and would have proudly walked across this floor in front of you.

Senator BROWNBACK. Laura?

Ms. DOMINGUEZ. I just prefer to show what's on the video.

Senator BROWNBACK. All right, that's fine. And we'll get to some questions——

Ms. FAJT. And I do have a video of me walking in France, just a month ago, and I believe you've seen it. And it was—I asked for it to be burned onto a DVD so that others could see it.

Senator BROWNBACK. We'll circulate that.

Ms. FAJT. So—but, obviously, I can do much better now than I could then.

Senator BROWNBACK. Very good.

Mr. Turner, Dennis Turner, was a Parkinson's patient. We heard from his doctor, Dr. Levesque, in the first panel. Mr. Turner, we're pleased to have you here at the hearing, and we'd look forward to your testimony.

STATEMENT OF DENNIS TURNER, SAN CLEMENTE, CALIFORNIA

Mr. TURNER. Thank you, Senator.

Thank you, Chairman Brownback, for your interest in Parkinson's disease, in my treatment by Dr. Levesque, and my hopes and concerns for the future.

For 14 years, I've had Parkinson's disease. This irreversible disease involves the slow destruction of specialized cells in the brain, called dopamine neurons. By early 1991, I suffered extreme shaking on the right side of my body, stiffness in my gait and movements. After some years of medication, I developed fluctuation and poor response to Sinemet. This made daily activities needing the coordinated use of both my hands hard or impossible, such as putting on my contact lenses. My disability prevented me from using my right arm.

Other than my Parkinson's symptoms, I was physically very active and fit. Because of this, Dr. Levesque felt that I'd be a good candidate for experimental treatment. He explained that he would take a very small tissue sample from my brain, removing its adult neural stem cells. He would then multiply and mature these cells into dopamine neurons, and then inject these cells back into the left side of my brain, which controls the right side of my body. He proposed treating only the left side because it controls the right side of my body, the side with the most severe Parkinson's symptoms.

Dr. Levesque did not tell me that this treatment would permanently cure my condition. Science has yet to learn what causes Parkinson's disease, much less how to remove it. However, since this cell-replacement approach had never been tried in a human patient, we hoped for the best. And since my only other realistic alternative was to continue growing worse til I eventually died, I decided to have the surgical procedure in 1999, one to remove the tissue, and another to inject the cells. I was awake for both procedures, under local anesthesia.

Soon after having the cells injected, my Parkinson's symptoms began to dramatically improve. My trembling grew less and less, until, to all appearances, it was gone, only slightly reappearing if I became upset or nervous.

[Laughter.]

Mr. TURNER. Which I am. I don't have as nice a name as you.

[Laughter.]

Mr. TURNER. Dr. Levesque had me tested by a neurologist, who said that he wouldn't have known that I had Parkinson's if he met me on the street. I was once again able to use my right hand and arm, and enjoy normal activities that I had given up hope of ever doing.

Since being diagnosed with Parkinson's disease, my condition has slowly, but continuously worsened. I can't say with certainty what my condition would have become if Dr. Levesque had not used my

own adult stem cells to treat me, but I have no doubt that, because of this treatment, I have enjoyed 5 years of quality of life that I feared had passed me by.

Last year, after 4 years of being virtually symptom free, my Parkinson's symptoms began reappearing in my body's left side. Today, I have various degrees of trembling in both hands, although I feel that the left is slightly worse. Nevertheless, I would not hesitate for a second to have Dr. Levesque use my stem cells to treat me for a second time, since, in my case, they were safe, effective, and involved no risk of rejection.

Because of my improvements through Dr. Levesque's treatment, I've been able to indulge in my passion of big-game photography these past 5 years. While on safari in 2001 in Africa, I scrambled up a tree to avoid being run over by a black rhinoceros. And you've got to be fast for those babies.

[Laughter.]

Mr. TURNER. I swam in the South Atlantic—that's off South Africa—with great white sharks. This was not cage diving; this was snorkeling with them. Two weeks ago, I returned from Africa after photographing cheetahs and leopards in the wild. Here are a few examples of the pictures I took—which I forgot to bring them, but they're nice pictures.

[Laughter.]

Mr. TURNER. Pictures I took. They represent memories and experiences I feel I have Dr. Levesque to thank for.

I came here to offer him my sincere gratitude, and to offer others with Parkinson's disease a concrete hope for—reason for hope.

This summarizes my history with Parkinson's, and the positive effects I experienced through a treatment that used my adult stem cells. I am very happy with the results, and would dearly love to have a second treatment. And, Mike, you can do it tomorrow. I'll be there.

Thank you, sir.

[The prepared statement of Mr. Turner follows:]

PREPARED STATEMENT OF DENNIS TURNER

Thank you, Chairman Brownback, for your interest in Parkinson's Disease, in my treatment by Dr. Levesque, and in my hopes and concerns for the future.

For fourteen years I've had Parkinson's Disease. This irreversible disease involves the slow destruction of specialized cells in the brain, called Dopamine Neurons. By early 1991 I suffered extreme shaking of the right side of my body, stiffness in my gait and movements. After some years of medication, I developed fluctuation and poor response to Sinemet. This made daily activities needing the coordinated use of both hands hard or impossible, such as putting in contact lenses. My disability prevented me from using my right arm.

Other than my Parkinson's symptoms I was physically very active and fit. Because of this Dr. Levesque felt that I'd be a good candidate for an experimental treatment. He explained that he would take a very small tissue sample from my brain, removing its adult neural stem cells. He would then multiply and mature these cells into Dopamine Neurons, then inject these cells back into the left side of my brain. He proposed treating only the left side because it controls the right side of the body, the side with the most severe Parkinson's symptoms.

Dr. Levesque did not tell me that this treatment would permanently cure my condition. Science has yet to learn what causes Parkinson's Disease, much less how to remove it. However, since this cell-replacement approach had never been tried in a human patient we hoped for the best. And since my only other realistic alternative was to continue growing worse until I eventually died, I decided to have the surgical

procedures in 1999, one to remove the tissue and another to inject the cells. I was awake for both procedures, under local anesthesia.

Soon after having the cells injected my Parkinson's symptoms began to improve. My trembling grew less and less, until to all appearances it was gone, only slightly reappearing if I became upset. Dr. Levesque had me tested by a Neurologist, who said he wouldn't have known I had Parkinson's if he had met me on the street. I was once again able to use my right hand and arm normally, enjoying activities that I had given up hope of ever doing.

Since being diagnosed with Parkinson's Disease my condition had slowly, but continuously worsened. I can't say with certainty what my condition would have become if Dr. Levesque had not used my own adult stem cells to treat me. But I have no doubt that because of this treatment I've enjoyed 5 years of quality life that I feared had passed me by.

Last year, after 4 years of being virtually symptom free, my Parkinson's symptoms began reappearing in my body's left side. Today I have various degrees of trembling in both hands, although I feel that the left is slightly worse. Nevertheless, I wouldn't hesitate for a second to have Dr. Levesque use my adult stem cells to treat me a second time, since in my case they were safe, effective, and involved no risk of rejection.

Because of my improvements through Dr. Levesque's treatment I've been able to indulge in my passion for big game photography these past 5 years. While on safari in 2001 I scrambled up a tree to avoid being run over by a Rhino. I swam in the South Atlantic with Great White Sharks. Two weeks ago I returned from Africa after photographing Cheetahs and Leopards in the wild. Here are a few examples of the pictures I took. They represent memories and experiences I feel I have Dr. Levesque to thank for. I came here to offer him my sincere gratitude, and to offer others with Parkinson's a concrete reason for hope.

This summarizes my history with Parkinson's and the positive effects I experienced through a treatment that used my own adult stem cells. I'm very happy with its results and would dearly love to have a second treatment.

Senator BROWNBACK. Thank you, Mr. Turner.

Dr. Goldstein is Chief Science Officer for the Juvenile Diabetes Research Foundation. This is a patient panel, but had requested to testify on this panel, so we wanted to accommodate you, Dr. Goldstein, on this panel.

STATEMENT OF ROBERT GOLDSTEIN, CHIEF SCIENTIFIC OFFICER, JUVENILE DIABETES RESEARCH FOUNDATION INTERNATIONAL (JDRF)

Dr. GOLDSTEIN. Chairman Brownback and Members of the Subcommittee, thank you very much for the opportunity to appear before you today. I'm Robert Goldstein, Chief Scientific Officer.

I am joined today by the Langbein family. I'd like to ask them to stand, please. Jamie was diagnosed with juvenile diabetes at the age of one. She worries about being different from her friends in school, and parents worry about the long-term complications of diabetes and their daughter's future, and whether their other children will be diagnosed with the disease. Jamie represents just one of the nearly two million people who battle juvenile diabetes each and every day.

Thank you so much for being here today.

Senator BROWNBACK. Yes, thank you for joining us.

Dr. GOLDSTEIN. JDRF is the leading charitable funder of juvenile diabetes research worldwide. Established over 30 years ago by parents of children with juvenile diabetes, our mission is to find a cure.

Over the years, JDRF has provided some $800 million in grants for diabetes research. To fund that science, JDRF volunteers do their part every day to raise money in their communities, and we

are proud of the strong partnership that we have developed with the Federal Government.

JDRF aggressively pursues all avenues of promising research. In Fiscal Year 2004, our commitments in the area of stem cell research totaled $8.2 million. Of this amount, $6.3 million is spent in the area of embryonic stem cell research, and less than $2 million on other areas, including adult stem cells. JDRF will continue to support both adult and embryonic stem cell research.

We appreciate that no one can predict what area will produce new therapies or a cure, and JDRF views adult and embryonic stem cell research as complementary pathways to our goal. Let me explain why, using pancreatic islet cell transplantation as an example.

In islet transplantation, the beta or insulin-producing cells are isolated from a cadaveric pancreas, and then infused into a person with juvenile diabetes. Once transplanted, these new islets begin to produce and release insulin into the patient's body. Since the year 2000, nearly 300 people have received islet transplants, and the majority of them lead significantly better and healthier lives.

These results are very exciting, but there are significant hurdles in moving this from an experimental procedure to a standard therapy. One such hurdle is the severe shortage of donated pancreases. In 2001, approximately 400 were available for islet transplantation and research, compared to the almost two million Americans with juvenile diabetes.

Here, then, is one reason why we are so excited about recent advances in embryonic stem cell research. Recent studies have demonstrated the ability to coax embryonic stem cells into insulin-producing cells in the lab. We have good reason to believe that embryonic stem cells will 1 day be able to grow large amounts of insulin-producing beta cells for transplant, but more work needs to be done.

Unfortunately, adult stem cells have not shown the same promise for diabetes. In a recent report, Harvard University researcher Doug Melton published a paper in *Nature* pointing out that, in mice, new beta cells in the pancreas are formed through the replication of existing beta cells, rather than through the differentiation of adult stem cells. This finding has important implications, especially if confirmed in humans.

In Type 1 diabetes, the autoimmune response destroys the beta cells. This means that in order to cure Type 1 diabetes, we'll have to rely on an external source of beta cells. Embryonic stem cells may well prove to be the main source for generating beta cells.

JDRF funds research to develop beta cells from adult stem cells, or to regenerate beta cells from existing precursor cells. Researchers have reported that human adult duct tissue might have the potential to develop into beta cells. Other groups have results that indicate that transplanted bone marrow cells may be able to show insulin production. Some have used these findings to argue that adult stem cells may be the answer for curing juvenile diabetes. JDRF takes the position that research using both embryonic and adult stem cells, perhaps in side-by-side comparisons, will get us to our goal fastest.

Mr. Chairman, JDRF recognizes that the science of producing insulin-secreting cells from either adult or embryonic stem cells is at an early stage. Given this reality, how can we adequately compare the effectiveness of adult and embryonic stem cell research unless both avenues are pursued simultaneously and with equal rigor? While we have made great strides toward our goal of a cure, more needs to be done, and we don't have time to wait. In the battle against diabetes, we are in a race against time.

To put the urgency of finding a cure into perspective, I'd like to share some words from Mary Tyler Moore, JDRF's international chairman, that she shared with Members of the House. Mary states, "In the nearly 6 years since human embryonic stem cells were first successfully cultured in a lab, diabetes has contributed to the deaths of as many as three million people and cost our Nation over $750 billion. It has caused nearly 500,000 amputations, rendered over 100,000 people blind, forced a quarter of a million people to require kidney transplants or dialysis. And 120,000 moms have been told that their child has Type 1 diabetes, a disease which, during that time period, would require each of these children to have 8,700 injections of insulin and 17,500 pricks of their fingers to check blood sugar levels—just for that child to survive."

Thank you, again, for the opportunity to appear before you today. I'm happy to answer any questions.

[The prepared statement of Dr. Goldstein follows:]

PREPARED STATEMENT OF ROBERT GOLDSTEIN, CHIEF SCIENTIFIC OFFICER, JUVENILE DIABETES RESEARCH FOUNDATION INTERNATIONAL (JDRF)

Chairman Brownback and members of this Subcommittee, thank you for the opportunity to appear before you today to participate in this important hearing on adult stem cell research. I am Robert Goldstein, Chief Scientific Officer of the Juvenile Diabetes Research Foundation (JDRF). I am joined today by the Langbein family who represent the millions of families who struggle with the daily challenges and fears of caring for a loved one with juvenile diabetes. Jamie was diagnosed at the age of one, and she has been on an insulin pump since the age of four. Jamie's diabetes affects her life every day, all day. Her parents must test her blood sugar eight times a day, and every time she eats, exercises, or goes to a birthday party, Jamie must account for what she eats or how much exercise she does and adjust her dose of insulin accordingly so she doesn't end up in the hospital or in a coma. Her mom gave up her career as an attorney so that she could always be nearby if Jamie had problems with her pump or blood sugar while at school, and her parents get up frequently during the night to check her blood sugar level. Jamie worries about being different from her friends in school, and her parents worry about the long-term complications of diabetes and their daughter's future and whether their other children will be diagnosed with the disease. This is just one child of the nearly two million people who battle juvenile diabetes each and every day.

JDRF is the leading charitable funder of juvenile diabetes research worldwide. Established more than 30 years ago by parents of children with juvenile diabetes, our mission is to find a cure for juvenile diabetes and its complications. Over the years, JDRF has provided some $800 million in grants for diabetes research at most of the world's leading universities, laboratories, and hospitals. To fund that science, JDRF volunteers do their part every day to raise money in our communities across the country—through walks, galas, and other events—and we are proud of the strong partnership for funding research that we have developed with the Federal government.

JDRF, as the world's leading charitable funder of diabetes research, aggressively pursues all avenues of promising research and makes its funding decisions based upon vigorous scientific review based, in many ways, upon the NIH model. In the area of stem cell science, JDRF funds scientists exploring the opportunities created by both adult and embryonic stem cell research. In Fiscal Year 2004, JDRF commitments in the area of stem cell research total $8.2 million. Of this amount, $6.3 million is spent in the area of embryonic stem cell research and less than $2 million

is spent on other areas of stem cell research, including adult stem cells. We focus on both areas—as well as dozens of other avenues of scientific investigation—because no one can predict what area of research will produce new therapies or a cure for juvenile diabetes.

Adult stem cell research has been pursued for more than 35 years, and as you know, embryonic stem cells were just discovered in 1998. JDRF will continue to support both adult and embryonic stem cell research so that we can pursue a cure as strongly as possible. However, the research community believes that embryonic stem cells offer more promise in the area of diabetes. Let me explain why, using pancreatic islet cell transplantation as an example. Islet transplantation has been a spectacular breakthrough in diabetes research. In islet transplantation, the beta—or insulin-producing—cells are isolated from a cadaver pancreas and then infused into a person with juvenile diabetes through a catheter inserted into the portal vein of their liver. Once transplanted, these new islets recognize blood sugar levels and begin to produce and release insulin into the patient's body. Islet transplantation had been attempted since the 1970s with limited success. However, in the year 2000, researchers made a breakthrough in the procedure, and since that time nearly 300 people have received islet transplants and the majority of them lead significantly better and healthier lives. In most of these individuals, therapeutic control of their diabetes has improved remarkably, and in many instances they do not even have to take insulin injections. Furthermore, many of the patients have reported a reversal in some of their complications, especially hypoglycemia unawareness but also improvement in vision and less pain from neuropathy.

These results are very exciting, but there are significant hurdles in moving this from an experimental procedure to a standard therapy that could benefit the millions of people with diabetes—many of them children. One such hurdle is the severe shortage of donated pancreases. In 2001, approximately 400 pancreata were available for islet transplantation and research, compared to the almost two million Americans with juvenile diabetes.

Here, then, is one reason why we are so excited about recent advances in embryonic stem cell research. Recent studies have demonstrated the ability to coax embryonic stem cells into insulin-producing cells in the lab. We have good reason to believe that embryonic stem cells will one day be able to grow large amounts of insulin-producing beta cells for transplant, but more work needs to be done. Unfortunately, adult stem cells have not shown the same promise when it comes to diabetes. Last month, Harvard University researcher Douglas Melton published a paper in *Nature* pointing out that in mice, new beta cells in the pancreas are formed through the replication of existing beta cells rather than through the differentiation of adult stem cells. This finding indicates that adult stem cells in the pancreas do not contribute to beta cell formation, and that embryonic stem cells may prove to be the only stem cells that will be useful to generate beta cells for the treatment of Type 1 diabetes. Other studies indicate that mouse embryonic stem cells can be differentiated into insulin-producing cells, and several studies suggest that this can be done using human embryonic stem cells.

JDRF funds research to develop beta cells from adult stem cells, or to regenerate beta cells from existing precursor cells. Researchers have reported that human adult duct tissue might have the potential to develop into beta cells. Other groups have results that indicate that transplanted bone marrow cells may be able to show insulin production. Some have used these findings to argue that adult stem cells may be the answer for curing juvenile diabetes. JDRF takes the position that research using both embryonic and adult stem cells, perhaps even in side-by-side comparisons, will get us to our goal fastest.

Mr. Chairman, adult stem cells may one day prove to be the answer to alleviating the pain and suffering caused by certain diseases—I certainly hope that is the case. We have heard some remarkable stories from some of the witnesses today. But we have no idea of knowing which diseases those may be, and unfortunately we are not certain of the widespread application of these treatments. We do know that to date, adult stem cells have not been shown to hold as much promise for juvenile diabetes as embryonic stem cells. Given this reality, how can we turn our backs on other exciting research opportunities, such as embryonic stem cell research, thereby potentially delaying life-saving therapies and cures for millions of people? And how can we adequately compare the effectiveness of adult and embryonic stem cell research unless both avenues are pursued simultaneously and with equal rigor?

We are in an extraordinary time of opportunity in the area of medical research, and this country is leading the way. Scientists around the world agree that stem cell research holds tremendous promise for hundreds of millions of people. I applaud you for continuing to monitor advances in the area of adult stem cell research, and I encourage you to do the same for embryonic stem cell research. For certain dis-

eases such as juvenile diabetes, embryonic stem cells hold the most promise, and we can't afford to lose any more time.

While we have made great strides towards our goal of a cure, more needs to be done, and we don't have time to wait. Insulin is not a cure for juvenile diabetes, nor does it prevent the onset of complications such as kidney failure, blindness, heart disease and amputations. Diabetic retinopathy is the leading cause of adult blindness in the United States; ninety percent of patients have evidence of retinopathy after fifteen years of diabetes with approximately 25,000 new cases of blindness per year. Diabetes is also the leading cause of renal failure in the United States, accounting for forty percent of new cases per year. Greater than half of all patients with diabetes develop neuropathy, making diabetic neuropathy the most common cause of non-traumatic amputations and autonomic failure. In his or her lifetime, a diabetic patient with neuropathy has a fifteen percent chance to undergo one or more amputations. Mr. Chairman, in the battle against diabetes, we are in a race against time.

Not a day goes by that JDRF doesn't receive calls or letters or e-mail messages from mothers or fathers of children with type 1 diabetes asking "When will my child be cured?" On the one hand, it is extremely difficult to explain the pace of science, particularly to a mother whose five-year-old has to prick his finger six or seven times a day to test his blood sugar, who needs three or four injections of insulin every day, who is afraid to go to sleepovers or summer camp for fear of falling into a coma, and who is at constant risk of developing a host of complications that could cut short his life. But on the other hand, it is downright tragic to have to explain how the pace of science could be slowed even further by focusing on one area of research and excluding another.

To put the urgency of finding a cure into perspective, I'd like to share some words from Mary Tyler Moore, JDRF's International Chairman, that she shared with Members of the House. Mary states that "in the nearly six years since human embryonic stem cells were first successfully cultured in a lab, . . . diabetes has contributed to the deaths of as many as 3 million people and cost our Nation over $750 billion. It has caused nearly 500,000 amputations, rendered over 100,000 people blind, and forced a quarter million people to require kidney transplants or dialysis. And 120,000 moms have been told that their child has Type 1 diabetes—a disease which during that time period would require each of these children to have 8,700 injections of insulin and 17,500 pricks of their fingers to check blood sugar levels—just for that child to survive."

Thank you again for the opportunity to appear before you today. I am happy to answer any questions you may have.

Senator BROWNBACK. Thank you. And I want to thank the Juvenile Diabetes Foundation for all the funding and the advocacy work that they're doing. A number of families in my state, constituents and friends, have children with juvenile diabetes, and I appreciate the work that you're doing.

I've got some questions I want to ask. Let me start, if we could, with Mr. Turner, if you don't mind. Please describe where you were before your treatment, the adult stem cell treatment. Just describe to me, in your words, what you were functioning like.

Mr. TURNER. I had extreme shaking of the right hand. I had difficulty writing my name. I had difficulty drawing concentric circles. Dr. Levesque took films of me before and after the surgery.

Senator BROWNBACK. Could you do the safaris and the traveling such as you have been doing?

Mr. TURNER. They were getting more difficult to do. And the second safari that I took was in 1999, after the surgery was done.

Senator BROWNBACK. You've said you were having a lot of difficulty, and then you had the transplant of your own adult stem cells from—grown outside of your body and then put back in.

Mr. TURNER. Yes, sir.

Senator BROWNBACK. What happened—what were you like after, and at the best point——

Mr. TURNER. I was functioning normally.

My walk was OK. My right and left hand were fine. Before, my right hand wouldn't swing when I walked. Then it started swinging after the surgery. I could put my contacts in. I could function normally. In fact, the neurologist that examined me said that everything—he wouldn't even have known I had it, if he had of not been told.

Senator BROWNBACK. And when did you get to that point in time after your surgery? How much time?

Mr. TURNER. About 6 months, Mike? Six months.

Senator BROWNBACK. And then—now, you've said that you've had some regression now that's taken place recently.

Mr. TURNER. Lately, about—oh, about 9 months ago, the symptoms started appearing in my left hand, my right hand started developing the symptoms again. And I just—it just regressed.

Senator BROWNBACK. And so you would like to be a candidate for a second round of this stem cell therapy.

Mr. TURNER. You bet your life. You bet my life, actually.

[Laughter.]

Mr. TURNER. You could bet your life, too.

Senator BROWNBACK. We're betting a lot of lives, because we want to get cures for this taking place, and you're showing some of the greatest promise of anything I've seen or heard about.

Mr. TURNER. I mean, when I was running from the black rhino in Zimbabwe, and, you know, you've got to head for a tree, you've got to be awful fast, because those things can really move. They don't look like they're fast, but they are. And when you photograph them, you always look for a tree or a rock to get up on. And I don't think I'd be here today if it wasn't for Michel, because that rhino would have caught me. So you've got to dive, you've got to do a lot of things awful fast. My physical abilities got better. I could do a lot more. And, just lately, I went to Africa, about 2 months ago, and I could feel a difference in my abilities than what I had before. I hope it's just not all age.

Senator BROWNBACK. Laura—and if your dad wants to answer these, that's fine, if you don't want to. And, Mrs. Dominguez is here with us, as well. Tell me, in your words, your progression, where you are now, and where you see yourself going. Where were you after the spinal cord injury at its worst situation, just in your words?

Ms. DOMINGUEZ. Well, right after my injury, I had regained, I guess some arm movement and some hand movement, and also some muscles in my abdomen. And I had no movement, like, in my lower body. So, I mean, as far as where I see myself, I mean, I'm going to get out of this chair.

Senator BROWNBACK. And you now have walked 114 feet, did you tell me that, in the testimony?

Ms. DOMINGUEZ. Oh, yes, that was a mistake. It was actually 1,400.

Senator BROWNBACK. Fourteen hundred feet?

Ms. DOMINGUEZ. Yes.

Senator BROWNBACK. Over a period of 30 minutes.

Ms. DOMINGUEZ. Yes.

Senator BROWNBACK. Is that correct?

Ms. DOMINGUEZ. Yes. With the braces.

Senator BROWNBACK. With braces. Were other people assisting you, or were you——

Ms. DOMINGUEZ. Yes.

Senator BROWNBACK. Is that—was that you doing most——

Ms. DOMINGUEZ. I had some assistance. Like, my dad will help, because the braces are really heavy. So——

Senator BROWNBACK. And with physical therapy—on the physical therapy you've emphasized a great deal. So apparently the stem cells can reunite and start the process, but then you've got to retrain the body——

Ms. DOMINGUEZ. Right.

Senator BROWNBACK.—is that the process, basically, you're in now, is retraining the body to move? And I see your muscles have atrophied, obviously, extensively from lack of use. You've got to build the strength back up in those, as well.

Susan, how about yourself. Now, again, where were you when you hit the lowest point, and where are you now?

Ms. FAJT. Well, the lowest point was obviously when I went flying through the roof of a house and got paralyzed.

Senator BROWNBACK. From where down?

Ms. FAJT. From level T7, thoracic 7, down.

Senator BROWNBACK. OK, describe that.

Ms. FAJT. The chest, right where you're at—chest level, down. Right here——

Senator BROWNBACK. OK.

Ms. FAJT.—down. And, as of now, I have sensation all the way down to my toes, and I have my abdominals, I have my hip flexers, which help me to walk with my braces, which I can do unassisted with my braces and a walker, for approximately an eighth of a mile, or longer and without—nonstop.

Senator BROWNBACK. Nonstop——

Ms. FAJT. Nonstop.

Senator BROWNBACK.—and nobody assisting you.

Ms. FAJT. Nobody assisting me. And I have my thigh muscles, my calves, my toe—if I concentrate while right in my bathtub and just stretching and trying to get my toes to move, I can do that, as well. Sensation is a major factor here. That comes first. It also comes with bad. There's—you know, I can obviously feel pain in my lower back at times, and especially after I exercise for extensive periods of time.

What was your other question?

Senator BROWNBACK. You've pretty well hit it. Where the two—where you were and where you are now. I understand where we're going. This is full-scale——

Ms. FAJT. Yes, and——

Senator BROWNBACK.—full mobility——

Ms. FAJT. Right.

Senator BROWNBACK.—no assistance——

Ms. FAJT. Right.

Senator BROWNBACK.—where we're headed to, and I have no doubt you're going to make it.

Ms. FAJT. Thank you.

Senator BROWNBACK. I want to go another round if we could afterwards, but Senator Wyden?

Senator WYDEN. Thank you, Mr. Chairman.

And Laura and Susan and Dennis, it is just a thrill to see your tenacity. I mean, I think that you just, you know, summed it up, Laura. You just put it out bluntly, you're going to get out of the chair, and that's, of course, exactly the kind of inspiration that people are looking for. And I'd just say God bless to each of you.

And I have only one comment. I mean, the three of you, you know, aren't politicians. I mean, you're people who just want cures. You want cures. You want your government to get serious about it. And I think, to me, Susan, it really comes down to the point you made at the end of your testimony where you talk about what legislators would do if it were our family.

Ms. FAJT. Yes.

Senator WYDEN. I've got a 15-year-old daughter, Lily.

Ms. FAJT. Right.

Senator WYDEN. I think the reasons that I'm here—and you haven't heard me say boo about Democrats and Republicans. That's not the way I approach this.

Ms. FAJT. Right.

Senator WYDEN. I'm here because I think to give more people a chance at success, the kind of accomplishments that you're talking about, we've just got to take the shackles off our scientists.

Ms. FAJT. And you can——

Senator WYDEN. We've got to——

Ms. FAJT.—do that.

Senator WYDEN. You get we can. And that's what a lot of us are trying to do in the Congress. And, unfortunately, that's what's been seen by some as political. But, to me, it's about science, and it's about responding to your question. You've laid it out. The Congress can do it. It's a question of political will, it's a question of the right policies, and it's a question of the right funding. I want you to know I'm going to do everything I can, not as a Democrat or somebody in a political party, but because I think it's right, because I think that's the answer to the very appropriate question you gave.

Dr. Goldstein, one question for you for this round. You heard the three patients. And I think, again, Susan, you put it very well, this whole spectacle of having to traipse all over the globe in order to get care, that's a disgrace. That's just wrong.

Ms. FAJT. Yes.

Senator WYDEN. In a country as strong and rich as ours, that shouldn't happen. My question to you, Dr. Goldstein, is, Don't we run the risk, as a nation, of having more patients and families having to make those around-the-world journeys with these policies that restrict research and work in this area?

Dr. GOLDSTEIN. The research is very actively going on outside the United States. We would prefer—JDRF would prefer that it geared up in the traditional fashion that NIH functions so that much more of the research could go on here. That would produce therapies that will be acceptable and regulated and useful within this country. And this is one of the few examples where outside the United States seems to be stimulated in more ways.

Senator WYDEN. Well, I think that—the reason I asked, I think—again, I don't want to approach this in a political fashion—is that I do think that the research restrictions will contribute to addi-

tional cases of the kind of problem that Susan described, and I want to see that changed.

A question I also want to ask for you, Dr. Goldstein, I asked Dr. Weissman, that embryonic stem cells can be used in a variety of tissues, and he indicated to me that adult stem cells end up being more restrictive, in terms of the tissues in which it can be used. Do you essentially share that view, as well?

Dr. GOLDSTEIN. Yes. People have been studying adult stem cells for more than 30 years. They've been trying to create insulin-secreting cells. That has not occurred. Embryonic stem cell research has already demonstrated that at a proof-of-concept level. So we would argue that—let's pursue everything that's promising as quickly and as urgently as possible.

Senator WYDEN. Well, I think—and I'm going to have to go in a second—I think sums up how I approach it. Let's pursue everything, and with exactly the kind of urgency you're describing. And I think that's what the American people deserve, and that's certainly what the people in my state are saying. And I'd just say God bless to each of you.

Thank you, Mr. Chairman.

Senator BROWNBACK. Thank you.

If I could, Dr. Goldstein, I was just given a note that Diane Faustman, Harvard, used adult cells, recently, from the spleen in diabetic mice, and the researchers in their paper noted permanent reversal of the disease. They're attempting to get some funding for clinical trials. Are you familiar with this work that they're doing? And——

Dr. GOLDSTEIN. Yes, sir.

Senator BROWNBACK.—what do you think of it?

Dr. GOLDSTEIN. Oh, it's terrific. It's proof of something in animals that needs to be translated to people. We hope it works.

Senator BROWNBACK. Are you doing some of the funding on this work, too, or do you know—maybe you don't——

Dr. GOLDSTEIN. I can't publicly respond.

Senator BROWNBACK. OK. It just seems to me that it's one of those promising areas. And what I'm trying to do is find areas that we can have successes that we don't have the controversy surrounding so that it's easy to move forward with.

Dr. GOLDSTEIN. Well, let me respond without saying any investigator's name. We're funding research to prove, confirm, reduplicate, and study those findings because we think they're important, as we are funding an encouraging research, as I said to Senator Wyden, in every area that seems promising. We think that you don't know the answer to a research question until you do the work. And so we don't want to stop, or not do, work until we get some answers, and that why we're—you know, just to repeat it, we're ecumenical, we want to support all promising avenues of research.

Senator BROWNBACK. You noted the need for donated spleens, is that correct, that you were—or, excuse me, pancreas donations——

Dr. GOLDSTEIN. Yes.

Senator BROWNBACK.—that some of that is occurring, but not near enough or as far as current knowledge and ability to get to the islet——

Dr. GOLDSTEIN. Right.

Senator BROWNBACK.—cells. Is that something that we should be pressing more from here?

Dr. GOLDSTEIN. Yes. Approximately 6,000-plus people die in the United States each year and donate organs. Now, many more people die and do not donate organs. But we're only able to acquire pancreases from maybe two thirds of that group.

Senator BROWNBACK. That donate organs.

Dr. GOLDSTEIN. That donate organs.

Senator BROWNBACK. Whereas, if everybody——

Dr. GOLDSTEIN. Well, if everybody—if everybody who died donated organs, there would be a lot of improvement for people to receive kidney transplants, heart transplants, lung transplants. There's a big, big need, very long waiting lists. So the organ donation issue has been around for a while, and the relative donation rate has been fairly flat, as opposed to increasing by 10 percent or 20 percent a year. So we'd love to have help to alert people to the benefits of donating more organs for transplant. That would help all kinds of people with all organs.

Senator BROWNBACK. And on juvenile diabetes, age is not an issue for—as far as the donated pancreas—because of the cells you're pulling out, or——

Dr. GOLDSTEIN. Well, there are some limitations, in terms of—once you get past 65 or 70, if you're an organ donor, sometimes those organs are less able to provide good quality islets. But, in general, there's a wide range of potential donors that the islets could be prepared from.

My point in the testimony was that, at our best, this week could maybe help 400 people with islet transplantations, and we have 30–40,000 people each year getting diagnosed with the disease, so that—that's a big disconnect, and we're probably not going to solve that problem by increasing organ donation, per se. That's why we need alternative sources for islets and beta cells, cells that secrete insulin.

Senator BROWNBACK. OK.

Senator WYDEN. Can I make sure I got that number straight? We can do three or four hundred now, and what's really needed, you said, are 30- or 40,000?

Dr. GOLDSTEIN. Right.

Dr. GOLDSTEIN. Newly diagnosed people with the disease, that number runs 30- or 40,000 a year. There are close to two million people with the disease today. The common feature is, they lack insulin-secreting cells. So if transplantation of insulin-secreting cells is to be a solution, 400 or 500 is not going to help that many people.

Senator WYDEN. I want to make sure I get the enormity of this, because I think what you're saying is just staggering. There are already two million individuals who are going to need this assistance, and every year we widen the gap dramatically. There are 300 people——

Dr. GOLDSTEIN. That's correct.

Senator WYDEN.—for whom you can get assistance, and it's 30- or 40,000 who need it on an annual basis.

Dr. GOLDSTEIN. That's correct.

Senator WYDEN. Thank you.

Senator BROWNBACK. Dr. Goldstein, let me ask you, are you familiar with the areas of work going on in the adult stem cell area on juvenile diabetes treatment?

Dr. GOLDSTEIN. I have some, yes.

Senator BROWNBACK. What do you—do you see some promising technologies developing there?

Dr. GOLDSTEIN. There's a lot of work going on to coax already-living cells to reduplicate. That's some form of regeneration or neogenesis from already-mature cells. That work is going on in encouraging pancreatic ductal cells to reduplicate, et cetera. The numbers that they're able to reduplicate into tend to be small, not huge.

Senator BROWNBACK. That's—the nature of the adult stem cell——

Dr. GOLDSTEIN. Right.

Senator BROWNBACK.—is, generally it's more controllable, but it's a slower-growing cell. Is that——

Dr. GOLDSTEIN. Well, the——

Senator BROWNBACK.—in multiplying?

Dr. GOLDSTEIN. It just doesn't create the numbers in experimental models that would be needed for widespread therapies. Today. Maybe tomorrow the data will look better. So like we support researchers to proliferate already-mature ductal cells, we support research to proliferate the few cells that are left, and we support work for an alternative source, a fresh source.

Senator BROWNBACK. I understand.

Dr. GOLDSTEIN. That's the idea.

Senator BROWNBACK. Mr. Turner—if I could, with the permission of my colleague, could I have Dr. Levesque come up and answer—what's Mr. Turner's status now? You did the treatment on him. And is there something that you would expect that he would get an additional treatment on? If you don't mind coming back up, Dr. Levesque, I would really like to pursue this, where you think Mr. Turner is now in his treatment, and what we need to do or to learn from Mr. Turner's treatment.

Dr. LEVESQUE. Well, what we've learned is that the treatment we gave Mr. Turner worked for 4 years, and his symptoms progressed more significantly on the side that was not operated than on the side he has been operated. We need to work on the dosage of cells to be implanted, the type of cells that need to be implanted. And that's why we need to do more clinical studies.

Senator BROWNBACK. In your clinical study that's coming up now that you're going, what are you doing different on this one that you didn't do on Mr. Turner's?

Dr. LEVESQUE. Nothing. It's going to be identical in the type of procedure and the type of implantation. There will be different dosage, however, in the next group of patients. There will be four different groups of patient receiving incremental dosage.

Senator BROWNBACK. Of different dosages, so you'll be able to——

Dr. LEVESQUE. Different number of cells, yes.

Senator BROWNBACK. Are you discouraged that, after a period of 4 years or so, some of the symptoms are returning? What do you give of that?

Dr. LEVESQUE. Well, you know, I think this is an observation that we need to evaluate scientifically, and I think we have to do more studies to understand the progression of the disease and the cause of the disease. Is it the number of cells we implanted initially? The cell survival? We don't know. There are factors that we did have a significant improvement of his symptoms at 6 months after the injection, and this persisted for several years. So I think we're on a right path to find some type of therapy and cellular therapy for this disorder. We still have a lot to find out on the course of the disease and the evolution of the disease with this type of therapy.

Definitely this type of therapy is—appears, anyway, to be better than the daily medication that are required by the hundreds of patient that have this disorder, and we are seeking alternative method to improve these patients. So we need to do more evaluation with this future group of patients.

Senator BROWNBACK. Are other people doing this same treatment regime and testing it through clinical trials?

Dr. LEVESQUE. Not this type of approach, as far as I know. There are other type of trials going on for Parkinson's disease, one of them using cells derived from the retina. And this type of cell secretes dopamine. But it's the same type of cells encapsulated to eliminate the rejection. At this point, I don't know the status of this clinical study.

So, at this point, this is the only study going on using neural stem cells for Parkinson's disease.

Senator BROWNBACK. Good.

Ron?

Senator WYDEN. Thank you, Mr. Chairman.

Again, Mr. Turner, we're just thrilled to hear about your success.

Mr. TURNER. Could I add one thing——

Senator WYDEN. Absolutely. Why don't you, and then I have questions for your doctor. Go ahead, please.

Mr. TURNER. This is just to you, in general, sir. The thing that amazes the most is, he injected the cells into the left side of my brain that controls the right side of my body; and my left side, at that time, was fine. My left side, right now, is far worse than my right side, and my right side showed the symptoms first. So something must be going on there. I don't know. If he doesn't know, no one knows.

Senator WYDEN. Well, I just think when patients fight and have the kind of tenacity that you've shown, that that's a big part of what treatment's all about and why you're such a good role model, and why we're glad and thrilled that you're here and you tell us about your progress.

Dr. Levesque, I want to ask you, though, a question with respect—you know, Parkinson's and this whole matter of embryonic stem cells being used in the research—when I asked you earlier about the comparison of adult stem cells and embryonic stem cells, you said—and I appreciate your candor—that you had not done work with respect to embryonic stem cells. And that, to me, was

important. May not be important to others, but that was important to me, in terms of the comparison, and particularly given the fact that you had been pretty critical, in your testimony, of embryonic stem cell research. My question to you is—a lot of advocates for cures to Parkinson's, a lot of the organizations, would like to see embryonic stem cells used to help pursue cures in this area. At least that's my understanding. Given that, do you, at any point, plan to try, even for the purpose of comparison—since you're making these statements about adult stem cells lines versus embryonic stem cells—do you, at any point, plan to even try to have some patients assisted with embryonic stem cells so that at least you could back up the kind of statement you made in your testimony today?

Dr. LEVESQUE. All right, let me comment to the first statement. My testimony is critical, from our aspect, of the perception and benefit of cell therapy in general, not only embryonic, but also adult. We have to understand where this type of therapy is in relation with other type of therapy, and I've mentioned that in my testimony, as well. And, as I mentioned, other avenues are potentially viable and successful beyond the cell therapy. So I was critical not only of this type of embryonic stem cell therapy, the are things that we don't know. There's a lot of noise and push to move on to embryonic stem cell therapy, but it's unknown what are the safety issues and benefit issue using these stem cells, the embryonic stem cell. I agree, we need to do more research, we need to compare both type of cells. Because the bottom line is that the embryonic stem cells will use the same pathways that the adult neural stem cell line will use to become differentiated neuron. So the embryonic stem cell can be used to become all kind of tissue. But you have to understand that the pathway to create the bottom neurons will be the same that we use for the adult neural stem cells. The risk and benefit of each of these type of therapy has to be evaluated.

The approach I use has the benefit to be autologous. It's the same tissue than the patient. Whereas, the embryonic cells, these are cells derived from other patients. We don't know the risk of immune rejections using this tissue. From other type of research, we know that there's an immune reactions when we implant cells or foreign tissue in the brain. So there are ways to evaluate and minimize these type of rejections. One company is encapsulating these cells with some type of substance, supposedly to minimize this immune reaction. Perhaps the nuclear cell transplant technology will also minimize the risk of rejection. We don't know. We need to do more research.

Senator WYDEN. Well, again, with all due respect, your testimony is quite critical on embryonic stem cell research, and it is not critical of adult stem cell research, and the reason I asked you the question about whether, at some point, you would be willing to look at embryonic stem cells for the treatment of Parkinson's is, I think that would certainly, in my own view—as a legislator who has spent a lot of time on science issues, that would be relevant to me.

Dr. LEVESQUE. I think—if I can answer—I quite think the current approved cell lines are inadequate to study these questions. And, obviously——

Senator WYDEN. So you favor changing the Federal Government's policy?

Dr. LEVESQUE. I think if the Federal Government——

Senator WYDEN. That's a yes or no question.

Dr. LEVESQUE. It is, yes. Because——

Senator WYDEN. You favor changing the Administration's policy——

Dr. LEVESQUE. Yes.

Senator WYDEN.—on stem cell research?

Dr. LEVESQUE. Well, no, don't change the policy. The policy is approving these cell—we have cell lines that have been approved for research; however, these cell lines are inadequate. We need new cell lines. So, yes, we need to add more cell lines to the current cell lines to answer these specific questions.

Senator WYDEN. Where would they come from?

Dr. LEVESQUE. Well, these have to be obtained from either embryonic IVF clinic that discard the tissue, or with the somatic nuclear transfer using an ovum from a donor.

Senator WYDEN. And you think all this can be done without changing Federal policy?

Dr. LEVESQUE. No, and we need to change the restriction on these cell lines, definitely.

Ms. FAJT. I agree.

Senator WYDEN. All right. So I think we're hearing something significant here. Dr. Levesque, you want to change Federal policy on stem cell research.

Susan, you want to change Federal policy on stem cell research?

Mr. Turner, do you think Federal policy ought to be changed? Just based on what you know.

Mr. TURNER. I would base my opinion on what Dr. Levesque said, because of his education. I'm educated as a mechanical/electrical engineer, so I don't have the basis of the research to make that kind of decision.

Senator WYDEN. Extra points for candor.

Laura, you want to say anything on this?

Ms. DOMINGUEZ. No.

Senator WYDEN. All right, you're off the hook, and spared.

I thank you all, and all of you have been very helpful. And, look, this is a field where there are differences of opinion. That's what I tried to talk about at the beginning. And, Dr. Levesque, you know, understand that I'm just thrilled with all that you've done for Mr. Turner. I mean, to have him come and to say what he said about you is thrilling.

I'm here because I want to change Federal policy, because I think there can a lot more people like these three wonderful witnesses that are at the table. And to do it, we've got to change Federal policy, take the shackles off our scientists, and let them do what they were trained to do, which is to be scientific advocates. They weren't trained to do politics, they don't have election certificates. They were trained to be scientists. And the Federal Government has held them back, and it's wrong, and that's why I and, I think, a lot of legislators of both political parties want to change it.

And I want to conclude by way of saying, to my friend Sam Brownback, who feels strongly about this subject and sees it differently, that I commend him for his fairness. He has always gone

out of his way to make sure that all viewpoints are aired on this. And to my friend Chairman Brownback, I say thank you.

Senator BROWNBACK. Thank you.

I want to thank the panelists for being here today on a panel discussing adult stem cells. And there are a variety of opinions on other topics which we've had numerous hearings in the Congress that could go into. And I've stayed completely away from and not engaged in this discussion because we really did want to focus on this particular area of adult stem cell research that I think we've had insufficient hearings on. What do we need to do to make further progress on these areas that are actually producing results and working today? What do we need to do on areas that we need to further get research on in the adult stem cell area that we all agree on and that we all agree is producing results? What do we need to do in therapies so that patients can get the treatments here rather than in Portugal? What do we need to do in therapy so that, once you get the treatments, you get the follow-up afterward, in care? And we could engage in the broader ethical debate, which has been raging for some period of time, and that would be fine, but it's not the point of what we've really tried to focus on today, of what can we do to support the real cures that we're seeing in front of us, and I want to see these treatments advance as much as we possibly can.

This discussion has been constructive. Sorry to have engaged some of you in a political debate when we were really just trying to look at the scientific treatments and issues that you've been dealing with. And I do hope, with all my heart, we're going to continue to move forward and make some real advances in areas that you're helping to frontier, and I believe, with all my heart, we will.

Thanks for joining us, all, very much. Thank you all, as an audience that has passions on this, for being a listening and not-participating audience. I appreciate that greatly.

The hearing's adjourned.

[Whereupon, at 4:55 p.m., the hearing was adjourned.]

A P P E N D I X

PREPARED STATEMENT OF FAYE ARMITAGE, JACKSONVILLE, FL

To All Members of the U.S. Senate:

Thank you for the opportunity to express the extreme urgency of the matter before you.

Since there undoubtedly are millions of others who will want to enter their testimonies into the Congressional Record, I will be direct so that I do not take up too much of your time.

Currently 3,000 people a day are dying from medical conditions which could benefit from stem cell research. Not rescinding the restrictions on stem cell research would be unconscionable.

Since transdifferentiation of adult stem cells has never been proven (according to Dr. Irv Weissman, leading adult stem cell researcher and many others), it is our moral obligation to expand the stem cell policy to accelerate embryonic stem cell research.

The suggestion that stem cell research is "killing human embryos" is misleading. The embryonic stem cells come from frozen blastocysts (fertilized eggs) from in vitro fertilization clinics, eggs that will be thrown away anyway by the IVF clinic (with donor consent) because they can no longer be used to create babies. Many of these fertilized eggs are defective/old, and so were not chosen for implantation—but can still be used to create stem cells. Is it better to trash them or use them to save lives? I'm sure that most sensible and rational people would agree that the latter option is moral.

Another frequently quoted adult stem cell researcher, Dr. Wise Young recently said this: ". . . at the present, embryonic stem cells are the only cells that have been shown to produce neurons when transplanted into the brain and spinal cord.

Can we do the above with adult stem cells? Maybe, but it will take longer to do this research with adult stem cells. Waiting is not an acceptable option for people with severe disabilities, particularly terminal neurodegenerative diseases such as Alzheimer's, Parkinson's disease, and ALS."

Now I'll explain my personal interest to accelerate ESC research: My 14 year old son Jason wants to be freed from paralysis and resume his life. Our family suffered the most unimaginable devastation when, at the age of seven, Jason became quadriplegic after a collision with another player on the soccer field.

Since the essence of life for a child is physical activity, Jason has all but lost his childhood. Every day, Jason is confronted with the unbearable pain of watching his four sisters' lives move forward, while he feels so terribly left behind.

Please don't condemn Jason and others like him to this continued suffering by not immediately expanding funding for ESC research. Jason desperately wants his life back!

Every day that ESC research funding is held up, 3,000 more people die from conditions that could benefit from stem cell research.

Thank you again for this opportunity to speak to you on the urgency of increased funding for stem cell research.

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