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PARKINSON'S DISEASE RESEARCH

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

ONE HUNDRED SEVENTH CONGRESS

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PARKINSON'S DISEASE RESEARCH

WEDNESDAY, MAY 22, 2002

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

The subcommittee met at 9:42 a.m., in room SH–216, Hart Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senators Harkin, Murray, and Specter.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Good morning, everyone. The Senate Labor, Health and Human Services, and Education Appropriations Subcommittee will now please come to order.

Three weeks ago, this subcommittee held a hearing on Alzheimer's disease, a condition that destroys the mind while leaving the body basically intact. Today we will discuss its biological opposite, Parkinson's disease, a condition that destroys the body while the mind stays fully aware of what is happening.

This is a devastating disease, as we will hear from our witnesses. But a cure is finally in sight. Scientists have made exciting advances against Parkinson's in the past year alone, particularly in the areas of embryonic stem cell transplantation, deep brain stimulation, and possible environmental and chemical causes of the disease. Many researchers believe that Parkinson's will be cured sooner than any other major neurological condition, possibly within the decade.

This progress would not have been possible without the National Institutes of Health, which supports 11 Udall Research Centers across the country, among many other efforts to cure Parkinson's. Senator Specter and I have led the effort to double funding for the NIH over 5 years, and I am proud to say we will complete that goal this year.

I am concerned, however, by the fact that NIH funding for Parkinson's has not kept pace with our doubling effort. This has occurred despite increasingly strong language in the Labor-HHS appropriations bills. So, I will pay close attention to NIH's plans for Parkinson's research in the years to come.

We have an outstanding panel of witnesses this morning. I would like to give a couple special welcomes, first to Don Schneider, who traveled here from my home State of Iowa to tell us about his experience with Parkinson's. Don, I thank you and your wife, Rita, for being with us.

Of course, I would like to welcome the greatest, to me the greatest athlete, perhaps one of the greatest human figures of the 20th century, Muhammad Ali.

Muhammad, your efforts to promote peace around the world and to help people in need are as legendary as your victories in the boxing ring. I know that I was, as much as anyone in this room and all over the world, so thrilled when you lit the torch at the Olympics. It brought back so many memories.

I think one of the great legacies, Muhammad, of your life and your career is you teach people never to give up. If you get knocked down, get up and come back again. I think that is the hope and I think that is the courage that you give everyone in this room and everyone who is afflicted with Parkinson's. We may have had setbacks, but we are getting up and we are coming back again. So, we thank you for giving us that courage and that leadership. We are honored to have you here today.

I also offer my warm welcome to Michael J. Fox. You may know him from Spin City and Family Ties or many successful films. But now that he has hit the New York Times Best Seller List with his memoir, titled Lucky Man, he may have found his true calling in being an author. Again, Michael Fox, thank you very much.

We are also honored and fortunate to have with us today three former Senators. Let's hear it for Claiborne Pell, our former Senator from the State of Rhode Island.

Next to him another great Senator, Charles Mac Mathias, of Maryland.

And he could not be here, but his better half and someone who we enjoyed being with for so many years and still do, Carolyn Long, wife of former Senator Russell Long.

Brock Adams was supposed to be here. I understand he is on his way, and I will introduce him when he arrives.

All four of these Senators have Parkinson's. We miss them greatly here in the Senate, but we are honored that you could be here today.

Finally, I would recognize one other special person, Ruth Kirschstein. Get ready, Ruth, because we have a surprise for you. Dr. Kirschstein began her career at NIH in 1956. She has held numerous positions there including Director of the National Institute of General Medical Sciences, Acting Director of the NIH, and her current position, Deputy NIH Director.

Ruth is a visionary and has been a tremendous leader during her service at NIH, playing a key role in launching the Human Genome Project and promoting women's health research. Throughout her career at NIH, there is one thing she has always paid particular attention to and that is the next generation of scientists, building up programs that encourage our best and brightest to enter the field of medical research.

So, it gives me great pleasure to announce this morning that Senator Specter and I, along with Chairman Regula and Congressman Obey in the House, have inserted language in the upcoming supplemental appropriations bill that will rename the National Research Service Awards program the Ruth L. Kirschstein National Research Service Awards.

Congratulations, Ruth, and thank you for your decades of service to our Nation. We look forward to many years of continued service at the NIH.

Now I would yield to my great friend, Senator Specter, for his opening remarks.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Thank you very much, Mr. Chairman, and good morning, ladies and gentlemen.

This overflow audience is a testament to the importance of curing Parkinson's. It is a matter which this subcommittee has been working on very hard for many, many years. As Senator Harkin outlined, we set out to double the funding for the National Institutes of Health. It has been moved from $13 billion to $23 billion, and the President has recommended in this year's budget an additional $3.7 billion; which will more than reach the doubling goal—possibly exceed our goal to double funding.

People ask what is next, and I say: "Well, the next step is to triple the funding for NIH."

We are a very wealthy country with a gross national product in the range of $10 trillion and a Federal budget in excess of $2 trillion. Also, it is a matter of establishing priorities, and there is nothing more important than health. The increase in funding has given the scientists the opportunity to do intensive research and clinical studies. The experts who appeared here recently from the National Institutes of Health on neurological diseases thought that we may have the cure for Parkinson's within 5 years. It is not a guarantee, but it is an estimate.

We face a very difficult challenge, ladies and gentlemen. Now pending before the Senate, and up for a vote in the course of the next several weeks, is a procedure called nuclear transplantation. It is commonly referred to as therapeutic cloning, and that is a misnomer. It is not cloning at all. There is an agreement against cloning to create another person, but when you have the procedure nuclear transplantation, it is accomplished by taking the DNA, for example, from a person who has Parkinson's so that the stem cell is consistent with that person and will not be rejected.

Regrettably the House of Representatives has criminalized this procedure which is, to my way of thinking, an absolute anathema, and we have to stop that in the U.S. Senate. When we have had crowds, audiences overflowing in this room on Alzheimer's and breast cancer and heart disease and many other ailments, Senator Harkin and I have sounded the bugle to have Americans tell their Senators not to criminalize an important medical procedure that may conquer so many, many diseases.

That is what we are calling on today.

There is a great deal more that could be said, but we have a very distinguished group of witnesses here today. As Senator Harkin has noted, we are especially grateful to Muhammad Ali and Michael J. Fox, who, when they come here, attract a lot of attention because there is so much admiration for what they have done. And that kind of attention stimulates public response to our call to influence Senators to allow us to continue the indispensable research to cure Parkinson's and many other maladies.

When The Champ took his bow, he looked pretty strong to me. He looked pretty resilient. I think he might still go 10 rounds under the proper circumstances. See, there he goes.

When we met in the back room, he walked in with Michael J. Fox, and I told him not to be too tough on Michael just because Michael was bigger and stronger than The Champ was.

And we thank Michael J. Fox for all that he has done. He has been in this room on many occasions and his efforts have been very instrumental in leading this subcommittee to move ahead with the funding for the National Institutes of Health.

So, we have come a long way, but we have got a long way to go, and our work is cut out for us. Anybody within sound of our voices, contact your Senators. Thank you.

Senator HARKIN. Thank you very much, Senator Specter.

Although not a member of the committee, she wanted to be here to recognize her perhaps most famous constituent, Senator Stabenow of Michigan.

STATEMENT OF HON. DEBBIE STABENOW, U.S. SENATOR FROM MICHIGAN

Senator STABENOW. Well, thank you, Mr. Chairman. I also am here as a family member of a grandmother who had Parkinson's disease and want to thank you very much for your leadership, Senator Harkin and Senator Specter. I am committed to do whatever we need to do to get the job done.

I am very much appreciative of the opportunity, before leaving to go preside over the session, to help introduce our most famous Michiganian in the world, from Berrien Springs, Michigan, Muhammad Ali and Mrs. Ali. Welcome. It is a great pleasure. We are very, very proud that you are Michigan residents. There is no question that from his career in the ring to his global diplomatic efforts to his many charities and philanthropic work, Muhammad Ali has been a role model to all of us. We in Michigan are particularly proud of that.

I did want to comment, though, that particularly in the days after September 11, when fear really threatened to divide all of us, I was very proud that it was Muhammad Ali who stepped forward and issued a call for unity and tolerance. So, in addition to all that you are doing, in addition to the fact that you are here today, I have quoted you frequently in saying: "Rivers, ponds, lakes, and streams, they all have different names, but they all contain water. So religions have different names, but they all contain the truth." So, I want to thank you for those words at a time that was very critical for our country.

You have fought a lot of battles in a lot of rings, and I know that you are here today to focus on your greatest battle, the fight against Parkinson's disease, one that you share with millions of Americans. We want you to know that for those of us here today, we are in the fight with you and we thank you very much for your heart and your strength and your courage. Thank you.

Senator HARKIN. Thank you very much, Debbie.

I would recognize Senator Murray for an opening statement and then Senator Wellstone.

OPENING STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman, and thank you to your leadership, to Senator Specter, and to all of the people here who are fighting for such an important cause.

As I have shared with you before, my father had multiple sclerosis and from the time I was 15 until he died a few years ago, my mother was his caregiver. We hold the hope that so many thousands of Americans do for research so that other families, other people do not have to live through the really tough, tough times that I have known and my family has known. But his spirit carries with me.

I share all your hopes and dreams that stem cell research will provide the answers for so many people. We simply cannot allow political decisions to jeopardize what is out there, the promise of hope for so many families.

So, thank you very much, and thank you to all of our witnesses today.

Senator HARKIN. Thank you, Senator Murray.

Perhaps one of our strongest voices and supporters in this fight against Parkinson's, my neighbor to the north, Senator Paul Wellstone.

STATEMENT OF HON. PAUL WELLSTONE, U.S. SENATOR FROM MINNESOTA

Senator WELLSTONE. Thank you. Thank you, Mr. Chairman. I am not a member of the committee, and it is gracious of you to let me make an opening statement. I will stay under an hour for my opening statement.

Senator Specter has been equally gracious.

I think the only thing to say is I want to thank you, Mr. Chairman, for your commitment. I want to thank the panelists, and of course, Mr. and Mrs. Ali and Michael J. Fox, and Joan Samuelson, whom I have known for so many years. But I would like to thank everyone else. I see Senator Pell here and I just want to thank all of you who are here today. Thank you for your courage. Milly, thank you for being here. There are so many heroes and heroines.

I think the one thing I want to say is that this hearing I approach with a sense of history because I do not think time is neutral, and I think it is terribly important. I had a chance to help write the Mo Udall bill, and we now have the Center of Excellence and the focus, but we need the resources. Time is not neutral. And everybody is here today to make sure that we have that research focus and that we find the cure. It is so important.

And none of this would happen except for the fact—look at this room, Mr. Chairman. Look at all of the men and women who have had the courage to tell their own stories. Joan, look how far this has come. But the whole point is to now have the resources and to have the focus and to find the cure.

I would like to thank everybody. It is an honor to be here.

Senator HARKIN. Thank you very much.

There is just one other person I'd like to recognize before I go to Dr. Penn to lead off our witnesses—someone who is really in the forefront of this fight, giving voice to it by writing a wonderful book

about his wife—Mort Kondracke. Mort Kondracke has been a great hero.

We also are blessed to have with us the former staff member of Senator Claiborne Pell, who is now the Senator from Rhode Island, Jack Reed. Senator Jack Reed is here with us too.

Now we will go to our witnesses. We have all of your statements. They will be made a part of the record in their entirety. I would ask if you could summarize your statements in less than 10 minutes. Then we can get into some questions.

STATEMENT OF AUDREY S. PENN, M.D., ACTING DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator HARKIN. Again, Dr. Penn is the Acting Director of the National Institute of Neurological Disorders and Stroke. She was named the Deputy Director of NINDS in 1995. Dr. Penn, welcome to the committee.

Dr. PENN. Thank you, Mr. Chairman. I am accompanied today by Dr. Diane Murphy, the Program Director in neurodegeneration, who is right behind me.

I would like to share with you the NIH studies and plans for Parkinson's disease. NIH and particularly NINDS have been heavily invested in supporting critical research in Parkinson's disease for over 3 decades. Indeed, over fiscal years 1996 to 2001, NIH funding for Parkinson's research rose by 126 percent and NINDS funding by 91 percent.

We have supported the research which delineated the usefulness of L-dopa, mapped the critical brain circuits affected by Parkinson's disease, and developed critical animal models. NINDS expanded these efforts by establishing the Morris K. Udall Centers of Excellence for Parkinson's Disease Research, and these centers include investigators who are working on almost every area identified as a priority by the Parkinson's Disease Research Agenda, which was developed in 2000, in collaboration with the research and advocacy communities, and we revisited it last January.

Parkinson's, as many of you know and as was said, is a debilitating neurodegenerative disease caused by progressive loss of dopamine nerve cells in the brain regions that control movement. Abnormal protein aggregates, which are called Lewy bodies, are seen in dopamine nerve cells, and cardinal clinical signs are tremor, rigidity, and slow movements.

Now, Parkinson's patients need therapies that can restore function and replace the missing nerve cells. Although levodopa, which replaces lost dopamine, restores function for a while, 75 to 80 percent of nerve cells are already lost when the first signs are evident. So, we need to protect, restore, and replace nerve cells in the specific brain centers.

So, important new evidence has emerged which is converging to shed light on how these cells are damaged. The availability of families with multiple members affected with Parkinson's allowed identification of genes, and then the defective proteins now known to be important to mechanisms of normal protein clearance and also to degeneration in Parkinson's. The abnormal proteins in the famil-

ial forms fold into aggregates, accumulate in and are toxic to dopamine nerve cells.

There is new evidence that rotenone, a commonly used pesticide which produces oxidative damage, also causes these proteins to aggregate, Lewy body-like aggregates, and damages dopamine nerve cells and causes severe loss of movement in rodents.

So, based on the better information on the mechanisms of damage, we have funded the infrastructure for design and testing of drugs that have the potential for protecting dopamine nerve cells against the causes of Parkinson's by slowing the degeneration, and drugs chosen on the basis of pilot studies will ultimately move into large clinical trials.

In the meantime, we are evaluating available results and promoting the clinical trials of deep brain stimulation, a surgical therapy that can achieve excellent control. DBS, however, involves implantation of electrodes into specific deep brain centers, and they have to be specifically implanted. It can be used on both sides of the brain, and it can restore nearly normal motor performance.

We have helped to design a study initiated by the Veterans Administration to compare best medical management with DBS in over 300 patients, and our funds will support the patients from the affiliated academic health centers to provide a larger and more diverse study group.

Now, cell replacement is another strategy for therapy in advanced Parkinson's, and we long have supported studies of embryonic stem cells from rodents in these studies. Investigators are now reporting success in driving murine pluripotent ES cells toward a neural fate and even to dopamine nerve cells. There have been a few successful reversals of motor disorders in rat models of Parkinson's simply by implanting undifferentiated mouse ES cells.

Fetal tissue transplantation demonstrated successful replacement of dopamine nerve cells in Parkinson's patients. There was no immune rejection, but very little impact on the clinical signs, and that is an absolute necessity. We must do that.

Our own intramural investigators have obtained approved ES cell lines, and are working to direct them to become dopamine nerve cells before investigating implantation either into the animal models or ultimately into human brain.

We are committed, within the President's stem cell policy, to encouraging investigators to expand these studies. Grant solicitations in areas such as gene therapy, stem cells, environmental and genetic risk factors, drug screening, and surgical therapies have encouraged investigators to apply their knowledge, and numerous new grants have been awarded.

We recognize that the Congress and the Parkinson's community have concerns about the level of funding provided to the implementation of the research agenda in light of the generous NIH and institute appropriations. We have actually invested more in Parkinson's research than any other of our major disorders, except stroke. However, workshops and planning for others of our disorders increase with increasing exceptional scientific opportunities for advances. And these disorders include epilepsy, multiple sclerosis, brain tumors, amyotrophic lateral sclerosis, spinal cord injury, muscular dystrophy, and autism. All of these demand attention.

Maintaining an appropriate balance among the many disorders within our mission continues to be a challenge.

PREPARED STATEMENT

So, we are extremely proud of the progress our investigators have made in the science of Parkinson's disease, which is already having an impact on therapy and ultimately will allow the cure. With all of the institutes across NIH, and with the collaborations with external advisors from the research and voluntary communities, we are confident of success.

So, thank you, Mr. Chairman. I will be pleased to answer any questions you have.

[The statement follows:]

PREPARED STATEMENT OF DR. AUDREY S. PENN

Mr. Chairman and Members of the Committee, I am Dr. Audrey Penn, Acting Director of the National Institute of Neurological Disorders and Stroke (NINDS). NINDS has a long history of supporting critical research in Parkinson's disease (PD), and we are currently leading the National Institutes of Health (NIH) effort to implement the Parkinson's Disease Research Agenda. We have exciting progress to report, and I am pleased to present some of the highlights of this work to you today.

BACKGROUND

Parkinson's disease, as many of you are aware, is a devastating and debilitating neurological disorder caused by the progressive loss of nerve cells that control movement. These cells produce the neurotransmitter dopamine, and their disappearance from the brain leads to tremors, rigidity, and slowing of movement. Other disabling effects can also occur, including speech problems and, in some individuals, difficulties with thinking, sleep, and depression. Parkinson's affects more than 500,000 Americans at any given time, and its severity varies from person to person. For some, the disease is marked by a rapidly debilitating physical deterioration, while in others, the disease can be managed for years with available medical therapies. Most people are diagnosed with the disease after the age of 50, although this disorder is not uncommon in younger people. All of these individuals need treatments that can control their disease and eventually a cure, and we are committed to continuing an intensified and coordinated effort to bring research to bear on this need.

For more than three decades, NINDS has been heavily invested in PD research. We have supported early studies of L-dopa, fundamental research on the brain circuitry affected by PD, the development of critical animal models, and important advances in understanding the genetic basis of parkinsonism. In the late 1990s, NINDS expanded these efforts by establishing the Morris K. Udall Centers of Excellence for Parkinson's Disease Research. Selected through a competitive review process, these Centers have proven to be a sound investment. Over the past several years, they have developed essential collaborations and have contributed to a wide range of research investigations, from the genetics of PD and cellular dysfunction of neurons in the disorder, to studies of brain circuitry, neuropathology, and preclinical testing of therapies.

As requested by Congress, and in light of the numerous opportunities in Parkinson's research, NINDS took its commitment to this field one step further, by leading the development of a multi-year scientific research plan for PD. As part of this effort, all components of the PD community came together to evaluate progress, reexamine plans and priorities, and identify critical research needs and new approaches with significant promise. NIH submitted this plan, the Parkinson's Disease Research Agenda, to Congress in March 2000. Although we are all optimistic that the Agenda will serve as a useful road map to developing and integrating treatments for PD, it is not possible to predict a precise time line for major breakthroughs or a cure for this disorder—even in a time of great scientific progress.

We believe that one of the most important results of developing the Agenda was that it highlighted the promise of many ongoing areas, as well as new opportunities in PD research, and the importance of accelerating progress in all of them simultaneously. To address these needs, NINDS and NIH staff have developed numerous grant and contract solicitations, consortia, and workshops that complement the in-

vestigator-initiated awards that make up the core of our grant programs. The number of NINDS-initiated PD research activities undertaken since the inception of the Agenda has far exceeded that for any other disease in the history of the Institute, and the number of NINDS staff working on PD has been expanded beyond that for other disorders within the Institute's mission. The scientific community has responded enthusiastically to these actions, and several significant research efforts have resulted, including the initiation of major clinical trials that we believe will have a significant impact on the treatment of Parkinson's—both in individuals who have just recently been diagnosed, and in those in the later stages of the disease.

DRUG THERAPY

For several decades, replacement of the neurotransmitter dopamine has been the mainstay of PD therapy. The delivery of the dopamine precursor L-dopa, as well as other drugs that stimulate the brain's dopamine receptors, have given many people symptomatic relief, enabling some to continue working and enjoying recreational activities for several years after their diagnosis. However, these treatments can come at a price—their effectiveness can diminish over time; they can cause uncontrolled movements and other debilitating side effects; and perhaps most importantly, they do not stop the continuing loss of nerve cells.

The identification of a therapy that could preserve dopamine neurons—a true neuroprotective agent—would be a watershed event in PD research. NINDS has now taken an important step towards addressing this urgent need, building on years of research to understand the disease at the molecular level. In September 2001, NINDS awarded funds to develop the design and infrastructure for a large trial of drug therapies believed to have the potential for slowing the loss of dopamine-producing nerve cells. In order to identify the most promising compounds for testing, NINDS solicited recommendations from academic and industry researchers, as well as from members of the advocacy community. Many drugs were suggested for consideration, and extramural experts, the trial organizers, and the scientific staff of NINDS developed detailed, objective criteria, in order to permit an unbiased evaluation of all suggestions. NINDS asked the committee to use this approach so that the selection of compounds for further testing would be based solely on their scientific promise. Following the initial pilot studies to determine proper dosing, safety, tolerability, and any preliminary evidence of benefit in Parkinson's patients, the most appropriate compound, or compounds, will be selected to proceed into definitive Phase III controlled trials. These studies are expected to enroll approximately 3,000 subjects at 42 testing centers. The results from the pilot phase of the project are expected within the next two years, but preliminary results from the Phase III trial are not anticipated until approximately 2010–11. This effort represents a significant commitment on the part of NINDS—one that will require an investment of approximately $40 million.

SURGICAL THERAPY

Even with the promise of new and improved drug treatments for Parkinson's, critical attention is also being focused on surgical therapies, especially for advanced PD. The U.S. Food and Drug Administration has recently approved deep brain stimulation (DBS)—the passage of electrical current through electrodes that are surgically-implanted in very specific brain regions, critical to motor control—for the treatment of advanced Parkinson's, and interest in this option is growing steadily. NINDS' commitment to the exploration of DBS as a therapy for PD goes back several years, and includes solicitations targeted to several technical aspects of DBS therapy. The Institute has now funded a number of investigators to study many basic questions about DBS, and we have assembled these researchers into a consortium that will meet for the first time in June 2002. In addition, NINDS is collaborating with the Department of Veterans Affairs (VA) on the largest clinical trial ever of DBS to treat PD. In this study, which will enroll approximately 300 subjects at six VA sites and affiliated academic institutions, researchers will compare stimulation of one of two different brain regions to best medical management of Parkinson's. If DBS is shown to be the more effective approach, subjects on medical management will also receive DBS—and the effects of the two different stimulation strategies will be compared. The results of the trial will address questions of critical importance to those affected by PD now, and NINDS support of the academic sites in this trial will enable the appropriate enrollment of both women and minorities in the study.

CELL AND TISSUE TRANSPLANTATION

For people with advanced PD, who have already lost many of their dopamine-producing nerve cells, replacement cell or tissue therapy is another promising strategy.

Studies of fetal tissue transplantation have already demonstrated that this approach is feasible in the treatment of PD, and advances in stem cell biology have made this therapy a future possibility as well. NINDS has long supported research on animal embryonic stem cells and adult stem cells, and some of this work has demonstrated success in reversing motor impairments in animal models of PD. We are committed, within the criteria of the President's stem cell policy, to expanding these studies further, and to aggressively exploring the potential of human embryonic stem cells in treating this disorder.

RESEARCH AGENDA IMPLEMENTATION AND SCIENTIFIC ADVANCES

These examples illustrate the types of targeted program activities that have already contributed to the implementation of the PD Research Agenda. Grant solicitations and workshops in areas such as gene therapy, stem cells, the cellular basis of PD, environmental and genetic risk factors, drug screening, and surgical therapies have encouraged investigators to apply their knowledge to the field of PD research, and numerous new grants have been awarded. Although NINDS has initiated a number of these activities, many other NIH Institutes and Centers (ICs) have also developed programs that are directly responsive to the needs identified in the Agenda. For example, the National Institute of Environmental Health Sciences (NIEHS) is currently developing a Consortium Centers Program, that will operate as a highly interactive national network engaged in research to understand the potential environmental influences in the causation of PD. In addition, multiple ICs participated in a joint exploratory grant program with several private PD research funding organizations.

While the initiation of these actions has been a critical part of our implementation effort, we recognize that it is ultimately the scientific output of the Agenda that will make a difference in the lives of people with Parkinson's. To that end, we have progress to report on a number of fronts:

—NINDS-supported stem cell researchers and their collaborators have found that mouse embryonic stem cells can develop into dopamine neurons in a rodent model of Parkinson's and help reverse impairments in motor function. Importantly, these cells exhibit their plasticity without any manipulation beyond implantation into the motor control regions of the brain. This work builds upon studies of the factors that can induce cells to become dopaminergic neurons, conducted over many years by NINDS intramural investigators and others, and it emphasizes the need to pursue stem cell applications within the federal policy.

—Although several genes that are involved in inherited forms of Parkinson's disease have been identified, the influence of particular genes on the more common forms of the disease is not fully understood. However, researchers have now conducted large-scale screening of the human genome and have identified several chromosomal regions that may be involved in PD. In particular, one study has identified small differences in the tau gene—which codes for a protein known to play a role in Alzheimer's disease and other neurodegenerative disorders—as a possible susceptibility factor for Parkinson's.

—While the influence of inherited genes on the development of PD has not been completely characterized, gene therapy is emerging as a promising technique for restoring function in animal models of this disorder. This work took a dramatic step forward two years ago, when NINDS-funded investigators found that the delivery of specific growth factors to primates with a parkinsonian condition, using a genetically-modified virus, could have dramatic reparative effects. Now a separate group of researchers has added to this armamentarium, demonstrating that a different virus—engineered to deliver enzymes critical for the production of L-dopa—can have similarly impressive effects in a rat model of the disorder. As researchers accumulate more information about the safety and efficacy of different delivery systems and treatment compounds, translational research on gene therapy for PD can move forward.

—NINDS and the National Institute on Aging have supported research that demonstrates exposure of rodents to the pesticide rotenone can cause the development of anatomic and behavioral changes that mimic those seen in PD. In addition, work supported by NIEHS has shown that other agricultural compounds can also produce abnormalities in cells that are similar to those produced by PD. This mounting evidence strongly implicates environmental toxicants in the development of PD, and along with the genetic contributions to the disease, establishes a framework for more extensive studies of risk factors and their cellular effects.

—Last month, intramural researchers at NINDS published a study showing widespread effects of PD on the sympathetic nervous system. This system controls functions such as blood pressure and heart rate—those we think of as automatic. Until this work was completed, researchers did not appreciate the extent to which the disease damages these nerves. Individuals with PD often experience symptoms such as orthostatic hypotension, or a drop in blood pressure upon standing, and the loss of sympathetic nerves observed in this study may help to explain why this occurs.

Despite the progress made by NIH-supported investigators, the task of implementing the Agenda will require our continued attention. A great deal of basic science research is still needed, and much of what is known must be moved along, so it can advance into the clinic. Our Institute is acutely aware of this need, and we are taking steps to facilitate translational studies across all areas of disease. We expect these plans will have a very positive impact on PD research, since many researchers in this community are poised to move their work into preclinical studies, and thus could take immediate advantage of such a program.

FUTURE PLANS

The most valuable outcome of the Agenda has been its use as a scientific planning tool. For the past two years, we have used the Agenda, along with the feedback we have received from the external scientific community through workshops and conferences, to guide our efforts. Since the start of the PD Research Agenda, NINDS has organized four meetings on different aspects of Parkinson's, and other NIH ICs have supported at least six others. The January 2002 Consortium meeting held at the request of Congress offered an additional opportunity for the research, advocacy, and NIH communities to engage in specific discussions about evolving needs in PD research. Among a wide range of suggestions offered by the clinical and basic science discussants, six emerged as priority areas from both groups:

—Participants encouraged NIH to strengthen translational, or bench-to-bedside, research. Translational projects are often quite different from research grants that test straightforward hypotheses about disease causation and treatment, and are at varying points of development along the basic to clinical research spectrum. For several months, NINDS has been developing a new grant program that will attract proposals that bridge basic studies with model development and preclinical evaluation of therapies, and will develop a framework in which these applications can compete more effectively for funding. We expect this program to be initiated in early fiscal year 2003.

—Participants also encouraged NIH to increase our understanding of how PD affects the dopamine systems of the brain. For years, NINDS-funded researchers and our own intramural scientists have been engaged in this work, primarily through basic science approaches to understanding the fundamental malfunctions in dopamine neurons that lead to their degeneration. We will continue to support this research, through investigator-initiated awards, as well as special solicitations and workshops, as critical new areas of biology are identified.

—To complement these efforts, participants recommended further expansion of research beyond the dopamine systems of the brain. This would include other brain systems and circuits that may be affected by PD, the effects of PD throughout the body, and the resulting non-motor complications of PD—which can range from depression and sleep disturbances to speech problems. NINDS is committed to supporting many aspects of this research, including continued exploration of the damage to sympathetic neurons caused by PD. An expansion of this work in all relevant research areas will likely require a trans-NIH effort.

—Despite the wide use of validated scales to assess outcomes, both NINDS and PD researchers in general have recognized the need for better biomarkers—biological indicators/tests of disease susceptibility, progression, or response to treatment. Certainly, our continued focus on the genetics of PD will lead to new ways to assess individual disease risk. However, early biomarkers of this risk and later markers of progression may be much more difficult to develop. NINDS will continue to fund improvements in imaging and other currently used techniques; however, the central problem in identifying new markers is our incomplete understanding of the disease process at the cellular level. For example, researchers in the Alzheimer's disease community understand how specific molecules are broken down in affected neurons—this offers hope for finding some of these molecules in the spinal fluid or blood. However, researchers have not fully characterized the degradation processes that take place in neurons affected by PD, and thus, we do not know if evidence of these processes can be detected

peripherally. NINDS staff is acutely aware of these difficulties, and will continue to evaluate mechanisms that can enhance and accelerate this research.

—Participants also recommended NIH support for preclinical studies of gene therapy, so that this research can move forward into clinical testing. We have already solicited applications on this therapy, and we expect that our efforts in encouraging translational research will also help in this regard. Further, once clinical studies are developed, we anticipate that the framework we have already developed in our clinical trials program, and our enhanced communications with the FDA, will facilitate the development of gene therapy approaches in PD.

—Lastly, the group recommended that NIH support improvements in animal models of PD, including small animals and non-human primates. We are already deeply invested in this work, and NIH-funded investigators have developed new animal models of PD since the start of the Agenda. However, we are committed to improvements in these models, and as a first step in the process, we have already engaged the extramural research community in discussions of how to facilitate the sharing of models that are currently available.

In the past two years, we have been successful in using the PD Research Agenda to guide our support of Parkinson's research, and this strategy has helped us to achieve the balance of investments outlined in the original Agenda. NIH estimates that PD research funding will be approximately $199 million in fiscal year 2002 and $215 million in fiscal year 2003. We believe that sufficient resources will be available to support the PD Agenda during this period, while NIH also attends to its many competing priorities. We will use both the recommendations from the original Agenda and those identified at the January and subsequent consortia meetings to guide the allocation of our resources in different areas of PD research.

We recognize that the Congress and the Parkinson's community have concerns about the level of funding that NIH has been providing for the implementation of the Agenda. Appropriations for NIH and its individual ICs have been extremely generous in past years, and Parkinson's research has clearly benefitted from this generosity. As a result, NINDS invested more of its fiscal year 2001 funds on PD research than on any other disorder except stroke, which has an incidence at least ten-fold higher than that of PD. However, workshops and planning efforts increasingly indicate that opportunities for research advances against problems such as stroke, epilepsy, multiple sclerosis, brain tumors, autism, spinal cord injury, muscular dystrophy and health disparities are abundant. Maintaining an appropriate balance among the many disorders within the NINDS mission is a challenge as the Institute moves toward the future. One hopeful note is that basic research applies to many disorders, and even research focused on a particular disease, has a bearing on many others. NINDS must capitalize on these synergies to most effectively carry out its mission in the coming years.

In closing, we are extremely proud of the progress we have made in accelerating research in Parkinson's disease, and we are grateful for the support of the Congress in these efforts. We do not have a cure yet, but we are initiating clinical trials that we believe will be critical to improving the treatment and quality of life of individuals with PD; we are developing a framework so that basic research can be effectively translated into treatments; and we continue to invest in essential basic science research—the foundation for all progress in medical science. We are not alone in these efforts. Many other ICs at NIH are involved in the implementation of the PD Research Agenda, and several voluntary organizations have expressed an interest in further collaborations. We will continue to work with other ICs through the NIH Parkinson's Disease Coordinating Committee, and with our external advisors and colleagues from the research and voluntary communities through the Parkinson's Disease Implementation Committee. With all NIH ICs and voluntary organizations working together, this undertaking can and will be successful.

Thank you, Mr. Chairman, for the opportunity to speak with you today. I would be happy to answer any questions.

Senator HARKIN. Thank you very much, Dr. Penn. We will go down through all the witnesses, and then we will come back for questions.

Next we have Dr. Ole Isacson, Director of the Center of Neuroregeneration Research and the Udall Parkinson's Disease Research Center at McLean Hospital at Harvard Medical School. Dr. Isacson is now an associate professor of neurology at the Harvard Medical School. Dr. Isacson, welcome.

STATEMENT OF DR. OLE ISACSON, DIRECTOR, CENTER ON NEUROREGENERATION RESEARCH, McLEAN HOSPITAL AND HARVARD MEDICAL SCHOOL

Dr. ISACSON. I want to thank you for inviting me and for your leadership on this issue. First of all, I would like to tell you that I am also very honored to speak about the exciting science that is possible through the work and the effort at the NIH. Beyond our science, it is also a human effort in that there is also a wonderful team spirit on this where the science has reached a level where we can actually make an implementation of a research agenda as Dr. Penn just mentioned.

With your permission, Mr. Chairman, I would like to use this chart to show some of the work on science that relates to this.

Herein lies the problem. This is the part of the brain that is called the midbrain, and in this part of the region here, about an inch across, you have something called the substantia nigra. Here you have the famous dopamine cells that everybody talks about that die in the disease. So, we have a few million here among trillions of nerve cells. The process of Parkinson's disease affects most of the brain, but only these cells here seem to be vulnerable. When you lose them, you get Parkinson's disease.

So, obviously from a very common sense perspective, you realize, as Dr. Penn mentioned, that preventing this degeneration, reactivating the cells, or replacing them is a very reasonable strategy. And I will show you in a couple of minutes here that that can be done.

So, this is what we teach at Harvard. So, what I am showing the Senators now is a drawing of how the brain works. It is known as a synapse, this thing here.

If you remember the million cells in the midbrain, each one of them sends about a thousand of these very microscopically small, less than we could ever see without a microscope, up in the front of the brain. They are these terminals where that release the dopamine. The Nobel Prize last year was awarded for people who understood that when you lose the dopamine here, you can take a drug L-dopa that gets accumulated here and sent out here into this brain region.

This is a very sophisticated element, and we scientists are trying to restore that one, and we are using every effort we can, all the scientific efforts we can, to restore this unit here. Most of the drugs that you currently can take as a patient relate to the understanding of this. But there are a number of new opportunities in restoring the function here, activating this element with growth factors, for example, which may become a home run, or any other analogy you want to choose, for Parkinson's patients.

This next shows the mechanism. As Dr. Penn mentioned, there are gene defects, the way the cell works, its energy metabolism called mitochondria, the proteins that were mentioned, the way they mess up the dopamine neurons and the way that leads to dysfunction of that particular cell. At each of these phases listed on this panel here, there are research advances. What we feel as scientists is we now need to translate those, make them real for the patients, and aggressively move forward to organize the scientific efforts.

There are many ways to organize that. This scientific chart here or this strategy here shows you some of these novel therapeutic approaches. They include what we call biomarkers. We need to be able to look at the brain and see what is happening both during the disease process and when we try restorative therapies. We are trying to prevent the disease as I mentioned previously, trying to keep the brain working, also replacing the cells, and also as was mentioned previously, we are using stem cells. This country is very well known—I am actually an immigrant—all over the world for its innovation and attention to discovery. We need a free science to be able to find the necessary treatments for Parkinson's disease, both using stem cells, understanding gene biology, and aging.

So, finally, to give you some evidence of that, thanks to the NIH Udall Center, the Udall bill, my team in Boston managed to translate some of these findings from stem cells into an experimental model of Parkinson's disease. What you see here on this panel is an imaging on the left side, but on the right side here you see implantation of mouse embryonic stem cells, and these stems cells differentiate into to the dopamine neuron that I told you was the core of the problem. So, in a prototype manner, we are already able to show in the laboratory that we have ways of obtaining the cell that dies in Parkinson's disease. Obviously these are prototypes, which means just like a new airplane or any new discovery, that we need a lot of work to move these things forward, and I look forward to describing some of the organizational methods, management that maybe can accomplish that.

So, if I may wrap up here, some of these concrete scientific studies do not only pertain to Parkinson's disease. Parkinson's disease, for reasons of its scientific promise, has spearheaded many other discoveries. When we make breakthroughs for Parkinson's disease, it is very likely that we will also make breakthroughs for ALS, Alzheimer's disease, and spinal cord degeneration. So, Parkinson's disease research is a way of opening doors to new therapies. Therefore, I feel very strongly—and most scientists and doctors feel the same way—that there is a real need to focus on this disease and do everything we can possibly to help and cure patients with Parkinson's disease.

PREPARED STATEMENT

This shared purpose we also feel with you as the Government and giving us the opportunity to do the research.

I would like to end my testimony there. If you have any further questions.

[The statement follows:]

PREPARED STATEMENT OF DR. OLE ISACSON

Senator Harkin and members of the committee, I am Ole Isacson, Director of the Neuroregeneration Laboratory, McLean Hospital and Harvard Medical School, and the NIH/NINDS funded Udall Parkinson's Disease Research Center of Excellence. The research center I direct is dedicated to basic research on the prevention and treatment of Parkinson's disease and neurodegenerative diseases. For Parkinson's disease, we have developed models for new treatments with cell replacement and transplantation of embryonic stem cells. We have shown that we can reduce parkinsonism in several experimental models that I will describe to you. In particular, I would like to emphasize that over the last few years with the available Udall bill, the activities that these centers have created throughout the United

States, and there are 11 of them, is considerable. The work on Parkinson's disease treatments and possibly cures is an achievable goal with effort placed in science and medicine. It is my opinion that there is an opportunity to increase the funding for Parkinson's disease research to reach the next technological level, which would include treatments. A strong research effort can be funded further to grow research centers and to grow national core facilities to provide service to smaller research groups across the nation and internationally to reach their scientific and therapeutic goals for Parkinson's disease faster. In particular, by building such an effort, we will increase the capacity not only for achieving treatments for Parkinson's disease, but there will be several measurable and meaningful results for the treatments of neurodegenerative diseases such as Alzheimer's, Huntington's and Amyotrophic Lateral Sclerosis (ALS; Lou Gehrig's disease), to mention a few, as well as spinal cord damage.

One of the most successful drug therapies for any neurological disease is L-dopa for Parkinson's disease. This was made possible primarily through the insights of scientists and clinicians, who in the late 50s and early 60s used the information obtained from animal and pathological studies to provide patients with a treatment. My laboratory's approach for Parkinson's disease is based on the idea that the degenerated dopamine neurons can no longer provide synapses in which the drug (L-dopa) can be converted and released in regular amounts into the striatum, where dopamine receptors translate this into neuronal firing and activation of the striatum. L-dopa and dopamine analogues, while initially helpful, eventually become insufficient with debilitating side effects for the patient. Since this loss of efficacy is likely due to continued loss of synaptic control, the homeostatic mechanism of transmitter release, the reinnervation with synapses by implanted or regenerated dopamine neurons can potentially provide a better intervention than drugs alone. Many practical issues remain before it becomes a standard and reliable therapy. Hopefully, scientific insights about new donor cell sources, as are described here, their axonal integration and connections will provide patients with a useful therapy. Clearly, it is necessary for these scientific discoveries to be matched by technical developments in neurosurgery to achieve that translation into useful clinical practice. Rapid progress seen in developmental biology, molecular biology, as well as technical developments of neurosurgery can further accelerate achieving regeneration and repair for a large number of neurological patients in need.

Typically, without any pharmacological treatment, a person afflicted with Parkinson's has a stiff posture and slightly unstable gait, with the arms trembling. In addition, many with Parkinson's disease experience emotional difficulties in dealing with the disease, but do not feel that their minds are otherwise affected. The instability in their posture, the masked face, the gait disturbance, the speech disturbance and the poor dexterity are very incapacitating. This type of patient was first described coherently by James Parkinson (1755–1824) in an essay "On the Shaking Palsy" (1817, Sherwood, Heely and Jones, London, England). In the United States alone, there are now at least a million Parkinson patients, and approximately 1–2 percent of persons above age 65 will get the disease. Nationwide, drug therapy alone costs about $6 billion per year and the cost of hospital care and other consequences associated with a person having Parkinson's disease are estimated at $25–50 billion per year.

Like Alzheimer's disease, Parkinson's is a disease that may happen in younger people, but the risk increases dramatically with age. This is probably because many of the cellular systems in the brain are difficult to renew or regenerate by themselves. While there are trillions of nerve cells in the brain, when nerve cells start degenerating as we get older it becomes harder and harder for the brain to compensate for the loss of these cells. For instance, in Parkinson's disease the symptoms are caused by the selective loss of a relatively small population in the brain consisting of approximately 500,000 dopaminergic cells. They are situated deep in the midbrain in a place called the substantia nigra, literally the black substance, caused by melanin seen in those neurons. In any brain that grows older, some of these dopaminergic neurons will dysfunction over time. The rate at which they die or dysfunction is individual. For certain people, whose rate of dopaminergic cell loss is slightly higher than normal, the likelihood that they will eventually lose the critical 85–90 percent of the cells that are needed for normal function is high. The brain somehow manages to compensate for a loss of about 85 percent of these cells, but when only a small number of functional dopamine cells or less remain on each side of the brain, the symptoms of Parkinson's disease appear. The neurotransmission that takes place at the nerve terminals that produce dopamine is necessary for all of us to initiate movements and without it, we freeze up and become unable to move.

The pharmacological substitution therapy provided by L-dopa revolutionized the treatment of Parkinson's disease. The neurosurgical treatment (pallidotomy) now became uninteresting to many clinicians, as it was hoped that L-dopa was a sufficient treatment for Parkinson's disease, and moreover, that this type of pharmacological substitution would be possible for all of the other neurodegenerative diseases. It turned out that the solution wasn't so simple. After 5 to 10 to even 15 years of treatment, the L-dopa became less effective, and not in the manner of normal drug-induced tolerance. As is now well known, the patients experienced severe fluctuations in the drug effect, despite relatively constant levels of the drug in the blood and the brain. The so-called "OFF" phenomenon describes a time when the drug somehow becomes ineffective for the patient. At such times, the patient freezes up momentarily and loses mobility. The "ON" times are when the drug works and the patient gains mobility. However, both the "ON" and" OFF" times may be adverse. Symptoms can fluctuate wildly with L-dopa treatment or analog drugs. During "OFF", freezing and rigidity and inability to initiate movement is then further compounded by side effects during "ON", such as extra, involuntary movements generated by the drug. These hyperactive movements and dystonia (abnormal muscle tension and postures) are debilitating. Given that these "ON-OFF" phenomena appear earlier and more prominently in patients with chemically induced Parkinsonism (such as due to MPTP toxicity), it seems probable that the more severe the damage to the dopamine system, the less likely it is that systemic drug delivery (oral administration of drugs, for instance) will be effective. Moreover, it is reasonable to assume that one of the reasons L-dopa becomes less effective is that it cannot be taken up by the decreased number of surviving dopaminergic neurons to create some form of regulated release of the transmitter.

This has led a number of scientists to question whether pharmacological drug substitution therapy will be effective for the age-related neurodegenerative diseases. If synaptic control and regulated release of a single substance is needed, then we may have to deal with the more complex issue of trying to re-create synaptic networks and/or preserve them from degeneration. Since the "ON-OFF" phenomena in Parkinson's disease are so debilitating, some neurosurgeons and neurologists found it worthwhile to explore pallidotomy once again in the 1990s. More recently, electrical stimulation of the subthalamic nucleus (DBS) has been shown to alleviate some of the movement disorder of Parkinson's disease. Another procedure, "thalamotomy", surgically removes a subset of neurons in the thalamus that participates in the parkinsonian tremor. Like all experimental methods, there is the need for an extensive evaluation of the effects.

In addition to the L-dopa or dopamine agonist drugs previously mentioned, and the neurosurgical treatment methods, there are a number of research efforts to prevent or treat Parkinson's disease. Some centers are involved in locating so-called susceptibility genes for Parkinson's disease. Although there seems to only be a small proportion of Parkinson's patients with a genetic component, certain genes may make it more likely to develop Parkinson's disease. If the disease is multifactorial, susceptibility genes may lower the threshold for developing the disease. Some scientists also indicate that there may be a heterogeneity among susceptibility genes, such that different genotypes may develop the same Parkinsonism. And as we have previously discussed, the disease is age-linked and therefore a number of biochemical changes occurring naturally by age may interact with the genes at various times. Such genetic research, in combination with new methods in molecular biology, may give us tools to develop preventive treatments.

As previously discussed, when dopamine is so severely reduced in the caudate putamen that Parkinsonism appears, we can give patients a precursor of dopamine, L-dopa, to reverse some of the loss of dopamine in the brain. This was first reported by Birkmayer and Hornykiewicz (Wien Klin. Wochenschr. 73, 787–788, 1961). Along with the discovery that L-dopa substitution worked in the early phases of Parkinsonism, the last 35 years of neurological research has provided us with a number of drugs that can either mimic the action of dopamine (analogs/agonists), block its uptake from the synapse (re-uptake blockers) and stimulate its release or inhibit its metabolic removal. In addition, other neurotransmitter-related drugs that interact with dopamine in the caudate and putamen have been used. The outstanding discovery that the precursor to dopamine (L-dopa) will provide symptomatic relief for patients with Parkinsonism still remains with some minor modifications, the major drug treatment for patients. However, the fact that this drug and other similar drugs lose their effectiveness over time still remains the major problem with Parkinson's disease. It is unclear at this time whether optimization of the dopamine agonist effects can provide an effective long-term treatment for Parkinsonism, even if new receptor agonists are developed. The question therefore

remains whether it will be necessary with synaptic replacement in the striatum to reverse the course of advanced Parkinsonism.

In cell culture and animal studies, it has been shown that brain-derived neurotrophic factor (BDNF) can help dopaminergic neurons against toxic insults. Similar effects have been obtained by infusions and increased supply of glial-derived neurotrophic factors (GDNF) by somatic gene therapy. If research is directed towards appropriate delivery of such substances to patients at risk for developing Parkinsonism or patients with accelerated cell loss in the substantia nigra, it is likely that some benefits could be derived. Moreover, by this kind of research we may find other substances that could mimic the effect of trophic factors and therefore help prevent the degeneration in the substantia nigra and other vulnerable brain regions. It is my overall impression that basic neurobiological research towards understanding the mechanism involved in neuronal death, and of dopaminergic neuronal death in particular, are well-underway and very focused. It is likely that these studies will yield sufficient insight to develop new clinical therapies. A word of caution in this regard, though, is that while clinical trials may be initiated, it could be some time before they are refined so that they can be available to a large number of Parkinson's patients.

The evolving science and therapies for brain disorders may develop in parallel with insights about the brain's own capacity for repair. In fact, the brain is probably the most adaptive organ at a structural level for continuous change and signaling, as well as morphological adaptation to functional demand. I am therefore convinced and very optimistic that new technologies and therapies can be developed through scientific research to cure Parkinson's disease. A national effort and increased funding for such work would provide the stimulus to take advantage of these unique opportunities at this time.

Senator HARKIN. Thank you very much, Dr. Isacson.

Now we turn to the driving force behind almost all of this, Joan Samuelson, president and founder of the Parkinson's Action Network.

A lawyer for many years, she was diagnosed with Parkinson's in 1987. Mrs. Samuelson has testified before this subcommittee more than 10 times, and we are proud and privileged to have you back again. Please proceed.

STATEMENT OF JOAN SAMUELSON, FOUNDER AND PRESIDENT, PARKINSON'S ACTION NETWORK

Ms. SAMUELSON. Thank you so much from the bottom of my heart, Mr. Chairman, Senator Specter. Your visionary leadership on this subject has benefitted our community of a million Americans with Parkinson's disease beyond measure, and giving us the opportunity to be heard and the work you have done to help our cause we are deeply grateful for beyond anything I can describe, and thank you so very much.

My testimony today I see as a story of hope. It is about hope that is essential, and it is a story about failed hope in the past and hope that we hope will be able to be realized in the future and should be. Hope is an ingredient that, to someone who has been diagnosed with Parkinson's disease, is as essential as food to continue living.

When you walk out of a doctor's office with a diagnosis of Parkinson's disease, your foundation has been taken from you because you are told you have a progressive, degenerative, chronic motor disorder that will only get worse. But there is wonderful medication that now will enable us miraculously to walk into a room and testify and drive our cars and work in the world and live with dignity.

But we also are told that those cells are continuing to die, as Dr. Penn said, 75 to 80 percent of them are already gone, and that cell

death and cell shutting-down is continuing relentlessly and that there is no solution to that right now.

What that means is we have a disease for which we cannot hope that we are going to outlive the odds, that we are going to beat the odds because there are not any odds to beat. There is not such a thing as remission. There is not such a thing as perhaps some combination of chemo and radiation that causes us to be labeled a survivor and be able to march in parades with that label. We know that we are going to eventually become prisoners of our bodies, unable to move and speak and swallow and die before our time. And yes, Parkinson's does kill.

So, what we have to do is cling to what is raw hope. What we have now, as Dr. Penn and Dr. Isacson were describing and as we heard in the scientific briefing at our public policy forum yesterday, is that our hope is now a verifiable expectation. Parkinson's is no longer called incurable. It is curable. What that means for us is that we can hope with something more concrete, but what we need is for that hope to be realistically matched with the opportunity to realize the scientific results from the promise that these scientists have been describing. And therein lies the dilemma that I want to talk about.

My testimony needs to be, I think, a bit of a report card. In 1999, we had the tremendous honor, Michael and I, of testifying before this committee, and at that point scientific promise was great and on the basis of that and on the basis of that hearing and your leadership, the scientists in the country involved in Parkinson's research teamed up with the National Institutes of Health and created the Parkinson's Disease Research Agenda, an historic document that laid out a road map to realize that promise and that hope with a cure, with some curative therapy that would rescue these million Americans or as many of us as the science could realistically rescue with enough money. And so, the science was laid out and a price tag was put on it of $1 billion over 5 years. And the clock began to run.

That research agenda was set in the year 2000, and as this committee knows so well and as we have come back to you and discussed it, it has not been funded. There are scientists that come to us and speak to our gatherings and describe the enormous promise, but their extreme frustration with the work that could be done that is not being done. The consequences of that are great and real and human.

What it means is that we have people for whom hope is fading. We cannot take care of those for whom hope has died, and we have lost people in the 3 years since 1999 and it grieves us. The father of our advocacy director, Lynn Phillips from Mississippi, many people who are gone or who are completely prisoners of their bodies. And hope is fading terribly for people like Milly Kondracke who sits behind me.

We should try to save Milly. It may not be possible scientifically, but it could. And we must try, it seems to me, as a country if we have that potential. And there are many others for whom hope is still there and it is strong, but we know we are in trouble.

Three years ago I described going to see Mo Udall and that being my future. I am still doing well, relatively, for 16 years post-diag-

nosis, and I am so deeply grateful for that, but I wake up every morning just about as frozen as he was when I went to see him. And some day that pill I take will not work, and that day may be soon. And I so desperately want, as every one of these other people in this audience and the rest of the million Americans, our country to make the investment that it must because the science is there to benefit not just us, but people with the other disorders that Dr. Isacson described.

PREPARED STATEMENT

We know it is a difficult problem, but we believe that with the leadership of the Congress, working with the National Institutes of Health, that the money is there and that it must be spent because hope is real and realistic now. Given that, it would be a crime to let it fade.

So, thank you for your leadership and your vision. I just ask that we work together on this next difficult but doable step. Thank you.

[The statement follows:]

PREPARED STATEMENT OF JOAN I. SAMUELSON

My testimony must begin with our thanks on behalf of the entire Parkinson's community to this Committee, for this hearing, for the opportunity to be heard, and for your leadership on our behalf. We are deeply grateful to Chairman Harkin, Senator Specter and the members of the Committee to help ensure that this dreadful disease is conquered as soon as humanly possible.

I also would like to recognize several members of the audience who have gone to great lengths to be here. First, joining us today are three former Senators who have Parkinson's disease, the Honorable Claiborne Pell (D-RI), Brock Adams (D-WA) and Charles Mathias (R-MD). Also joining us today is Mrs. Carolyn Long, wife of Former Senator Russell Long (D-LA), who also has Parkinson's. I know they share our message today.

Also present are Lynn Fielder from Palo Alto, California, and her nine year-old daughter, Maya. Maya recently wrote Senator Harkin, explaining how her mother's life may depend on an increased federal commitment for Parkinson's research. Her letter will appear in the Congressional Record today. Thank you all for being here.

I seek to persuade this Committee of three things. First, the cost of Parkinson's—human, financial and otherwise—is too great to endure. Second, it is now possible to take concrete steps to stop it. Third, that it requires the federal government to honor a commitment made two years ago, to fund development of a cure thoroughly and aggressively.

So there are many reasons for our plea to you today. Our message today is one of huge human suffering, dazzling scientific promise—and a failure of our government to translate that promise quickly. It is inexpressibly sad, but true. Parkinson's is waging a war in the brains of the million of us diagnosed, and the several million more Baby Boomers and others who have pre-symptomatic dopamine cell loss. This war will take an unacceptable number of victims. We have weapons sitting in the warehouse. And—by government choice—we are meandering to a cure.

This is, in a way, a progress report, given almost three years after our first report to this Committee in September 1999. It is a hard thing to do for two reasons. First, it requires that we tell tales of the failure of hope. That goes against every instinct of those of us diagnosed with a chronic progressive disorder of this magnitude: with such news, the only way to go on living is to keep our spirits alive, which requires hope—the food on which the spirit feeds. So, we believe the cure will come—in time for each of us.

The brutal reality of Parkinson's degeneration, however, is that as more and more dopamine neurons shut down, we require more and more dramatic rescues, until the day when the system utterly fails to work. At that point, we are forced to recognize that hope is gone and give up our personal dream in favor of those with more time. In the three years since the 1999 hearing, I have watched hope fade in that way for many people. It is always a cruel thing to watch; sometimes it is lethal.

Take Lynn Phillips of Mississippi. He tried every experimental program, including a deep brain stimulation procedure that required his town to throw a huge chicken

fundraiser to pay for it. But finally, Parkinson's won: the death certificate presumably refers to complications secondary to his Parkinson's—but Parkinson's had so beaten him up that he had few defenses left.

And take Fred Zeiss of New York City, who was forced in recent years to put aside his career, and in his depression put on 100 pounds. It was the resulting heart attack that killed him, but his family says it was really Parkinson's.

Our office was hit hard this past year by Parkinson's deaths to the father of our Advocacy Director, John Rogers, who died last fall after brutal suffering; and the uncle of our Executive Director, Elisabeth Bresee Brittin, last winter. There are many others across the country, most of whom have not died, but live lives robbed of nearly every freedom they possess short of the freedom to think and dream. The stiffness and slowness of movement combine to cause the body to freeze up. At that point, the mind is encased as if in an iron lung, by an unyielding outer shell. That shell is us, though: the body is imprisoning itself. In those cases, it feels just about as cruel to watch them continue to live.

When I was diagnosed, I decided that I would never succumb to such a state. I still hold a profound belief that I will be rescued in time to keep my livelihood, my independence and dignity. But I have to admit that, more frequently than three years ago, I experience episodes of that final stage—when the available medications work poorly at best.

So where are we in fulfilling the desperate hope of a million Americans, and the approaching need of millions more? The science is full of promise: There is a dazzling set of cutting-edge biomedical approaches waiting to be applied. They include:

—High throughput screening of possible toxic agents and therapeutic compounds;
—Gene-environment initiatives using high tech testing;
—Applying information on proteins involved in Parkinson's genetics to understand the disease process;
—Imaging advances for earlier diagnoses before symptoms appear;
—Neuroprotection: applying all these advances to prevent cell loss in the healthy and protect those afflicted against further deterioration.

And, for the million-plus of us who need a therapeutic rescue, there is an equally dazzling array of new approaches:

—Cell restoration
—Cell replacement
—Gene therapy
—Viral vector technology
—Cell line creation technology, using techniques such as stem cells

The science of Parkinson's is at the front lines in all these areas. Eminent scientists are so optimistic that for years they have been predicting and quantifying the time remaining—highly unusual, and hopeful, behavior.

But precious little concrete movement toward completion of some curative treatment has occurred. It is not the fault of science. It is a failure of government to act. This is the second piece of the report that it hurts to tell.

I hasten to add that I do not fault this Subcommittee. It in particular has frequently expressed its concern and led initiatives that support Parkinson's research. In response to Congressional urgings, in 2000 the NIH convened a team of Parkinson's researchers who developed the Parkinson's Disease Research Agenda—a plan that called for a $1 billion additional investment in Parkinson's research over five years. Since the Agenda's development, the Congress—and especially this Committee—has urged the NIH in increasingly strong language to fully fund the Research Agenda. Every element for success seemed to be in place, including the process of "doubling" the NIH's overall budget by 2003, to ensure that a Parkinson's increase would not come at the expense of other disorders.

Despite these efforts, the federal commitment for Parkinson's is falling far short of the Agenda's targets. While each month brings further progress and new discoveries that could lead to a Parkinson's cure, the percentage of spending on Parkinson's research has not even kept up with overall NIH spending. In fact, in the two years since the Agenda was completed, there already is a $100 million shortfall in the NIH's spending on Parkinson's research. The numbers create problems in funding that we hear constant stories about: the many grant applicants with great ideas and high peer review scores, but where low funding scores kept them below the pay line.

At the root of the problem is an utter failure of leadership to implement a research agenda for Parkinson's. Despite some very hard working and wonderful scientists at lower levels, there has been an absence of vision and commitment at the top—of both the NIH and the key brain-related institute—which manifests in many ways. Despite huge opportunity for major strides in brain research, the NINDS directorship has been a revolving door for years. The institute's lack of focus and di-

rection has discouraged good candidates. The NIH hierarchy seems to regard the Parkinson's Disease Research Agenda as nothing more than a distant aspiration rather than an operational document that must be funded. However, scientific directors cannot make this happen without budgetary and policy commitments from the top. This situation is, without question, having the effect of delaying a Parkinson's cure.

For all these reasons, the road to a Parkinson's cure is a meandering one, with huge consequences. First and foremost, people with Parkinson's will suffer. That is simply not right. Americans with other disorders that seemed intractable—AIDS and cancer, for example—are alive because of the benefits of federal research investments. It should be Parkinson's turn. Moreover, the scientific and bio-technological advances that result unquestionably will speed breakthroughs in many other disorders.

So what is to be done? The Congress cannot allow this un-met promise to continue. We urge this Committee and the rest of Congress to use every available power to turn this around quickly. We urge the following:

—That the NIH Director use his transfer authority to commit $50 million for Parkinson's research this year;

—Full funding of the $197.4 million increase over the baseline year for 2003, year three of the NIH's five-year Parkinson's Disease Research Agenda, including significant funding of translational and clinical research;

—Complete the five-year doubling of the NIH's budget by providing $3.7 billion (for a total of $27.3 billion) in fiscal year 2003;

—Continue and expand the NIEHS budget, with an increase of $30 million in fiscal year 2003 for Parkinson's focused research;

—Work closely with the NIH to ensure that they aggressively implement the Parkinson's Disease Research Agenda.

It is the responsibility of the federal government to seize this opportunity and that of Congress to ensure that they do, including that the NIH be responsive to Congressional report language regarding Parkinson's funding. That's why your leadership is critical to ensure that the visionary Parkinson's Disease Research Agenda is regarded as an operational document that must be fully funded and implemented, rather than merely an aspirational document that is never truly realized.

We fear that we already have missed the opportunity to save some people by failing to fully fund the great scientific potential. But, if we act now, there are many others who can still be saved. With this Subcommittee's leadership, the future we dread will be rewritten into a history in which Parkinson's has been sidelined forever. That day can't come too fast.

Senator HARKIN. Thank you very much, Joan.

Don Schneider lives in Clinton, Iowa. That is on the Mississippi River, for those of you who do not know. It is the same town where he was born. He worked at radio station KROS for most of his career, eventually rising to general manager of the station, and President of the Iowa Radio Network, before Parkinson's disease forced him to retire 3 years ago. He is accompanied here by his wife, Rita.

Don, thank you for being here. As I said, your statement will be made a part of the record in its entirety. If you could just sort of sum up what you want us to know about how this has affected you and what you want us to do. Please proceed.

STATEMENT OF DON SCHNEIDER, PARKINSON'S PATIENT, CLINTON, IA

Mr. SCHNEIDER. Well, I would first like to say for an Iowa farm boy who was standing in a hayfield on Sunday, it is pretty overwhelming to be here in front of these bright lights and on this panel with these great personalities. In fact, I kind of feel as out of place as a faithful husband on an edition of As the World Turns.

But anyway, I guess I am here to put a human face on Parkinson's disease, and I figure Muhammad is providing the pretty face, so you will just have to put up with mine.

Fifteen years after my diagnosis, Parkinson's disease is continuing to slowly but surely chip away at my quality of life. It has

forced me to leave a job I loved, placed a heavy financial burden on my family, and at times each day leaves me unable to walk, read a book, or even dress myself. For someone raised as an independent farm boy, I cannot express the frustration that accompanies this type of disability.

As the Senator mentioned, I come from Clinton, Iowa. After graduating from high school, I attended radio school at Brown Institute in Minneapolis, and at the age of 19, started as a night announcer on a small radio station in Clinton, Iowa. I served in a number of capacities with that station, everything from an announcer to program director. In 1987, I purchased stock in the company and was named general manager.

Professionally I was active in the Iowa Broadcasters Association and, as the Senator mentioned, President of the Iowa Radio Network. I was also active in my local community as every small businessman is. I was a member of the Kiwanis Club, helped the United Way board of directors, served on the Substance Abuse Council, and was part of countless fund raisers for many worthwhile projects in the Clinton area.

I enjoyed working with young people. I was inducted into the Junior Achievement Hall of Fame for serving as an applied economics advisor. I coached junior football and basketball. Later I even took up the stripes as a high school basketball official.

It was in 1988, during a high school basketball game I was refereeing, when I held out my hand to indicate two shots, I noticed an uncontrollable shaking. Well, my family had also begun to notice a blank stare on my face, and I was experiencing slowness of movement and pain in my neck. One visit to the clinic and I was diagnosed with Parkinson's disease at the age of 35. For 5 years after my diagnosis, I hid it from all but my family. When people asked, I would simply say I had a neurologic disorder. As Michael Fox put it, you do not want to believe this is happening to you and you certainly do not want anyone else to know what is happening to you. You worry about what they will think, how they will treat you. It was extremely difficult, after being someone who was always in charge, to be forced to depend on others to help me.

At first, with the help of my medications, I continued living a relatively normal life, and as long as the medication was working, I could do just about anything. But eventually the progression of the disease and side effects of the medication left me no longer able to be fully functional at work, and my condition worsened to the point that I had to end my broadcast career and retire from the station in 1999.

Today I reside in rural Clinton County with our three youngest children. My two older children are now finished with school and living on their own. Katie, 21, is serving our country in the U.S. Army stationed at Fort Polk, Louisiana. My other daughter, the oldest, Sarah, graduated from the University of Iowa Hospitals and Clinics and is working as a registered nurse in the Neurology Department.

This is not to say that it has been easy. I can recall many profound sadnesses that I saw in the eyes of my family after the diagnosis and we all faced the uncertainty of what will happen in the future. I cannot deny that each day I worry about what the future

will be like. On one hand, I know there has been great progress made. There are new medications that have become available just in the 15 years that I have had Parkinson's disease. But there is still no known cause and the possibility of being trapped with an active, alert mind in a body you cannot control is a fate worse than death.

Since giving up my job, we have had to rely on my wife's income in an accounting firm and Social Security disability to get by. Fortunately, my wife makes a good living, but it has taken an economic toll on our family. We are facing the prospect of soon losing our health insurance with its prescription drug coverage. With a cost of over $700 a month for my prescriptions, this will certainly make us have to do with a lot less.

I often think about all my family has been missing and had to give up because of my diagnosis and condition with Parkinson's disease, and I have tried to channel some of that anger into the work I have done with a local support group in Clinton, Iowa. Our group of over 30 families has been a great help to me in facing the daily struggles of Parkinson's.

No one knows why or how I got this terrible disease. Is it genetic? Well, two of my great uncles did have Parkinson's disease, but one was on the maternal, the other on the paternal side. Does the environment play a role? I grew up drinking farm well water, but so did the rest of my family and none of them has Parkinson's. The bottom line seems to be we just do not know what causes this disease, but I am hopeful that we will have the answers soon.

I am not a quitter and I refuse to give up hope. I have always had a love of old cars. In fact, I keep a red Corvette in my garage at home right now. One of my mottos that I have tried to use all the time, dealing with Parkinson's disease, I stole from a movie called The Gumball Rally. As the race in that movie is about to start, a driver in a Ferrari turns to his co-pilot, tears off the review mirror, and says, "now the first rule of Italian driving—what's behind me does not matter."

I do try to keep looking ahead rather than worrying about what is behind me and remembering all that I have lost, trying to be thankful instead for my wonderful family and all that I have going for me.

PREPARED STATEMENT

Again, I thank you, Senator Harkin, and I am especially proud as an Iowan of your being awarded a second Mo Udall Award last night for your work for fighting against Parkinson's disease. And as The Champ might put it, with the help of all these great people, I cannot see how we will not whip this thing sooner or later. Thank you.

[The statement follows:]

PREPARED STATEMENT OF DON SCHNEIDER

Thank you, Chairman Harkin, for holding this important hearing today on Parkinson's research. As a fellow Iowan, I am especially honored to be here today to speak to you about Parkinson's disease—both the incredible toll it takes on its victims and their families—and the great urgency of providing the federal resources necessary to cure this dreadful disease.

Fifteen years after my diagnosis, Parkinson's is continuing to slowly but surely chip away at my quality of life. It has forced me to leave a job that I loved, placed a heavy burden on my family and at times each day renders me unable to walk, read a book or even dress myself. For someone raised as an independent farm boy, I cannot express the frustration that accompanies this disability.

Let me begin by giving you a little background about myself. I was born in Clinton, Iowa and raised on a farm in Mt. Carroll, Illinois. After graduating from high school, I attended radio school at Brown Institute in Minneapolis, Minnesota. At age 19, I went to work as a night announcer for KROS radio in Clinton. After serving in a number of capacities at the station—everything from Announcer to Program Director—I purchased stock in the company and was named General Manager in 1987. Professionally, I was active in the Iowa Broadcasters Association and served as President of the Iowa Radio Network. I was also very active in the local community—a member of the Kiwanis Club, helping the United Way's Board of Directors for the Clinton Substance Abuse Council and was involved in countless fundraisers for various worthwhile projects in the Clinton area. In addition, I have always enjoyed working with young people. I was inducted into the Junior Achievement Hall of Fame for serving as an Applied Economics Advisor. I have always had a deep love of sports, especially basketball. I tried to share that with youngsters by coaching junior football and basketball. Later, I even took up the stripes as a high school basketball official.

It was in 1988, during a basketball game I was refereeing, I held out two fingers to indicate two shots when I noticed shaking in my left hand. My family had begun to notice a blank stare on my face and I began experiencing slowness of movement and pain in my neck. One visit to the clinic and I was diagnosed with Parkinson's at the age of 35. For five years after my diagnosis, I hid it from all but my family. When people asked, I simply said, "I have a neurological condition". I could relate very well to the feelings expressed by Michael J. Fox when he was first diagnosed with Parkinson's. You don't want to believe this is happening to you and you certainly don't want anyone else to know what is happening to you. What would they think? How would they treat me? It was extremely difficult after being someone that was always in charge to be forced to depend on others to help me.

At first, with the help of my medications, I was able to continue living a relatively normal life. As long as the medicine was working, I could do just about anything. But eventually, progression of the disease and side effects of the medications left me no longer able to count on being fully functional at work. My condition became so unpredictable that I was forced to end my broadcasting career in 1999.

Today I reside in rural Clinton with my wife, Rita, and three youngest children, Joseph 17, Sam 14 and Anne 10. My two oldest children are now finished with school and living on their own. Katie, 21, is serving our country in the U.S. Army. She is stationed in Ft. Polk, Louisiana where she currently works with a mobile medical unit. Sarah, our oldest, recently graduated from the University of Iowa and is now at University Hospitals and Clinics working as a registered nurse in the Neurology Department—something that certainly takes on added significance given my condition. I am very lucky to have a strong, supportive family that has stood by me from the beginning.

That's not to say it has been easy. I can still recall the profound sadness in the eyes of my family members and the uncertainty and sense of dread we all felt when word came of my diagnosis. I cannot deny that each day I worry about what our future will be like. On the one hand, great progress has been made and many new medications have become available in just the short time I have been affected. On the other hand, there is still no known cause and the possibility of being trapped with an alert, active mind in a body I cannot control is more frightening than I can describe.

Since giving up my job, we have had to rely on my wife's income from her job at an accounting firm and Social Security to get by. Fortunately, she makes a good living, but there is no question that Parkinson's has taken an economic toll on our family. We are facing the prospect of soon losing our health insurance with prescription coverage. With a cost of over $700 a month for my prescription medication, we will certainly have to make do with a lot less. I often think about all that my family is missing because of Parkinson's Disease.

I have tried to channel some of my anger over being diagnosed with Parkinson's into something positive. I started a Parkinson's support group in Clinton several years ago, which I still facilitate. This group of over thirty families has been a great help to me in facing the daily struggle of life with Parkinson's.

No one knows why or how I got this terrible disease. Is it genetic? Two of my great uncles had Parkinson's—but one was on my maternal side and the other was on my paternal side. Does the environment play a role? I grew up drinking farm

water, but so did the rest of my family and no one else has Parkinson's. The bottom line is we just don't know what causes Parkinson's. But, I am hopeful that we will have answers soon. Scientists have made remarkable progress and with adequate funding could find new treatments and even a cure in my lifetime.

I am not a quitter and I refuse to give up hope. I have always had a love of old cars, and have used as a motto a line from an old car movie "The Gumball Rally". In that movie as the race is about to start, a driver in a Ferrari turns to his co-pilot, tears off the rear view mirror, and says, "now the first rule of Italian driving—what's behind me does not matter". I try to do the same. Keep looking ahead rather than worry about what I've lost and remember all I have to be thankful for—most importantly my wonderful family. I hope that by staying involved and active in the fight for a Parkinson's cure, I can make a difference in my destiny and that of the million other Americans suffering from this dreadful disease.

Again, I thank you for the opportunity to be here today.

Senator HARKIN. Don, thank you again so much, again for putting a real human face on what this means to families.

Now, as the most recognizable man on the planet, Muhammad Ali—we have already said a lot about him—certainly needs no introduction. He is simply the greatest of all time.

Lonnie Ali has been married to Muhammad for 14 years and has coordinated all his affairs for the past decade. Among her many activities related to Parkinson's disease, Mrs. Ali serves on the board of the Michael J. Fox Foundation for Parkinson's Research. We welcome you both here, and Mrs. Ali, again, your statement will be made a part of the record and Muhammad's will be made a part of the record. Please proceed as you so desire.

STATEMENT OF MUHAMMAD ALI, FORMER HEAVYWEIGHT BOXING CHAMPION

ACCOMPANIED BY LONNIE ALI

Ms. ALI. Thank you, Chairman Harkin. A little correction. I have been married to Muhammad 16 years.

I have to count every year.

But thank you and the members of the subcommittee for inviting Muhammad and me here today for this important hearing on Parkinson's disease research funding. We are grateful for your past support and for focusing attention on this important topic.

We were compelled to be here today because of the troubling situation we see occurring with regard to Parkinson's research, that may be unnecessarily delaying progress toward better treatments and even a cure for Parkinson's. We are here because Muhammad has never been one to sit back quietly and wait for things to happen. He is and always has been a fighter, not just in the ring, but with each and every cause he believes in. We are here today as champions of the National Institutes of Health research, who will not stop until we reach the gold, a cure for Parkinson's.

To the world, my husband is known as an Olympic Gold Medal winner, the Heavyweight Champion of the World, and a man who has always stood up for what he believes in. No matter what the cause, Muhammad has always used his charm and grace and wit to better the world. From the antiwar movement, to the fight for civil rights, to his efforts to raise awareness about the plight of many third world countries, Muhammad has never been far from the center ring.

Today, however, he is facing an opponent unlike any he has ever fought. Just as the million other Americans who suffer from Par-

kinson's, Muhammad is battling a relentless, remorseless, insidious thief. Parkinson's recognizes no titles, respects no achievements, nor bows to any amount of talent, courage, or character. Parkinson's does not discriminate. There is no question that Parkinson's is the fight of Muhammad's life.

But Parkinson's affects more than just those who have the disease. As the wife, friend, and confidant of someone who lives with someone with Parkinson's, I can tell you that our entire family and our close friends have been profoundly impacted as well. At this time in our lives, we had expected to be enjoying retirement, continuing to fight for important causes, and most importantly, enjoying time together as a family. Parkinson's never stops trying to rob us of those dreams. Even though Muhammad keeps punching back and refuses to go down for the count, we are certainly not living the life we had envisioned.

We often talk about how much more Muhammad would be doing to make the world a better place, to stand up for those who cannot stand up for themselves, to fight racism, and to spread his message of peace. There can be no doubt that Parkinson's is depriving not only our family, but the Nation and even the world of Muhammad's full contribution.

But Muhammad is only one man. There are 1 million Americans suffering from Parkinson's. Imagine what those million Americans could be doing to better the world if not for this disease.

While Muhammad and I keep up the fight on a personal level, scientists are fighting each and every day in laboratories across the country to find a cure. They tell us that Parkinson's is the most curable neurological disease. In fact, at a hearing before this subcommittee on September 28, 1999, Dr. J. William Langston, president of the Parkinson's Institute and a member of the scientific advisory board for the Michael J. Fox for Parkinson's Research, said: "While science is full of serendipity and unexpected surprises in research, sometimes you hit a point where it's time to focus. I truly believe that we are now at a point where there is enough knowledge that it is a time to focus. With a focused effort, the pieces are in front of us, the science is there. I think we can make major progress towards this disease."

We have reached a crossroads. We know the science is there but the money is not. I am proud to serve as a member of the board of the Michael J. Fox Foundation for Parkinson's Research. The foundation is doing tremendous work to fund incredibly promising private research. Now it is time for the Federal Government to get into the fight for real. We must provide the Federal funds necessary to carry out this promising research. As the world's leader in biomedical research, our Government has a responsibility to realize the tremendous scientific potential and provide adequate funding.

Two-and-a-half years ago, the NIH established the Parkinson's Disease Research Agenda, which called for a $1 billion increase in Parkinson's funding. Unfortunately, the Parkinson's agenda is not being fully funded. In fact, there is a $100 million shortfall for this year alone.

Time is of the essence. People with Parkinson's do not have any time to waste. This tragic underfunding may lead to missed oppor-

tunities for better treatments and even for a cure. Congress and the NIH have an opportunity to oversee effective treatments and possibly a cure for Parkinson's, if the necessary funding is made available.

Muhammad has never been one to do anything halfway, and he has never settled for doing something second best in anything that he has done, in the ring, in his work on humanitarian causes, or in his personal life. We implore the NIH and Congress to not go halfway on the Parkinson's Research Agenda. The Federal Government must aim high and work hard to reach the goal of finding a Parkinson's cure.

PREPARED STATEMENT

Our challenge to you today is to champion this research and to fully fund the Parkinson's Disease Research Agenda by committing $353.3 million for year 3. Together let us knock Parkinson's disease down for the count.

Thank you very much.

[The statement follows:]

PREPARED STATEMENT OF LONNIE ALI

Thank you, Chairman Harkin and Members of the Subcommittee for inviting Muhammad and me to be here today for this important hearing on Parkinson's Disease research funding. We are grateful for your past support and for focusing attention on this important topic.

We were compelled to be here today because of the troubling situation we see occurring with regard to Parkinson's research, that may be unnecessarily delaying progress toward better treatments and even a cure for Parkinson's. We are here because Muhammad has never been one to sit back quietly and wait for things to happen. He is and always has been a fighter, not just in the ring, but with each and every cause he believes in. We are here today as champions of National Institutes of Health (NIH) research, who will not stop until we reach the gold—a cure for Parkinson's.

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But Parkinson's affects more than just those who have the disease. As the wife, friend and confidant of someone with Parkinson's, I can tell you that our entire family, and our close friends, have been profoundly impacted as well. At this time in our lives, we had expected to be enjoying retirement, continuing to fight for important causes and, most importantly, enjoying time together as a family. Parkinson's never stops trying to rob us of those dreams. Even though Muhammad keeps punching back, and refuses to go down for the count, we are certainly not living the life we had envisioned.

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Our challenge to you today is to champion this research and fully fund the Parkinson's Disease Research Agenda by committing $353.3 million for year three. Together, let's knock Parkinson's Disease down for the count.

Thank you very much.

Senator HARKIN. Now the founder of the Michael J. Fox Foundation for Parkinson's Research, someone who has given us so much hope and encouragement and courage through his book and through his forming this foundation. This is Michael J. Fox's third appearance before this subcommittee. Mr. Fox, we welcome you back.

STATEMENT OF MICHAEL J. FOX, FOUNDER, THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Mr. FOX. Thank you and good morning. Mr. Chairman, Senator Specter, and members of the subcommittee, thank you for this opportunity to testify.

Is it just me or were you sitting in different seats the last time I was here?

Senator HARKIN. I am constrained to say it is "back to the future."

Mr. FOX. I apologize if that is a sore subject for some members of the subcommittee, but I bring it up only to make the point that it is a tribute to each of you that irrespective of the musical chairs of electoral politics and who sits in which seats on the dais, the subcommittee's commitment to biomedical research funding has remained consistent and committed. And we are very grateful.

Mr. Chairman, all Iowans and all Americans can be grateful and proud of your leadership on issues of health, including your continuing efforts to make biomedical research a higher national priority. You and Senator Specter have spearheaded the historic effort

that will soon succeed in doubling the budget for the National Institutes of Health over 5 years. The fact that you have done so, despite difficult budgetary time, changing administrations, and changes in majority control, underscores the notion that illness and injury truly are non-partisan issues that need bipartisan solutions.

I am grateful for the subcommittee's invitation but I would not have come back again if I did not feel I had something constructive to add. Although we appreciate this forum, none of us here today has any interest in becoming another of this city's self-perpetuating cottage industries.

Back in 1999, I testified that Parkinson's research was far ahead of the money, that high quality and high impact projects are being slowed down or stalled completely by the lack of available support. In addition to appealing to you and to the NIH, it was clear that there was more that we could do ourselves. It did not take long to find a group of like-minded people and together we launched a foundation with the single purpose of stimulating and supporting research, strategic thinking, and collaborations to accelerate the cure for Parkinson's.

We are committed to enabling the work of scientists, and to do so, we focus on the process of identifying, funding, and tracking research. We try to target where we can have the biggest impact and to employ the best methods to shorten the funding cycle, share the outcomes of research, and stimulate a coordinated effort to translate promising findings into a cure.

Some of our programs support investigator-initiated grants, the bread and butter of the NIH system and an indispensable mechanism for supporting new ideas. But with our emphasis on higher-risk, higher-reward projects, we have streamlined the NIH model and applied some of our own innovative thinking.

We have also enlisted scientists to identify the highest priority areas of research and recommend proactive steps we can take to move the field forward in meaningful ways. Such assessments have led to several specific funding initiatives, including a search for a conclusive diagnostic test or biomarker for Parkinson's, and development of a cell line specifically for the study and treatment of Parkinson's.

Last fall we launched a $2.2 million initiative to develop cell lines with characteristics deemed relevant to Parkinson's. As with our other programs, the scientific response was overwhelming. We received applications from a veritable who's who of cellular biologists worldwide. The number and the quality of the proposals compelled us to double the program's budget to $4.4 million, which made it possible for us to support a portfolio of projects exploring all the promising techniques for creating cell lines from adult, fetal, and embryonic cells. The number and diversity of these programs will allow for a meaningful comparison of these exciting technologies.

In our request for applications, we made it clear that we valued results over technique or cell source. Our program is to develop an effective tool to study and treat Parkinson's, not to support new technologies for their own sake or to pick favorites among emerging therapies. As any patient will tell you, their favorite therapy is the one that works. This is an obvious and logical approach if your goal

is to cure a disease, but often the political debate can lead to arbitrary decisions or otherwise obscure the fact that the goal of the research is to treat, heal, and cure.

I want to commend you, Senators Harkin and Specter, along with Senators Feinstein, Hatch, and all your other bipartisan colleagues, for supporting the Human Cloning Prohibition Act of 2002, which strikes the necessary balance between development of potentially lifesaving research and inappropriate applications of this powerful technology. It is important to make clear that the debate is not about promoting one type of research over others. It is about protecting researchers from being demonized or criminalized so they can go about their work exploring new opportunities to treat illness and disease.

Development of such promising new therapies puts us on the threshold of a new era of medicine. Today a neurologist may be able to do little more than tell you the name of the disease that is taking away your life, or in some cases he or she may be able to give you a prescription or two to ease the symptoms for a few years. It is not a great proposition, but there is a paradigm shift underway. Understanding of the brain and of neurological disorders is advancing at a staggering pace, moving from definition of the disease, to treatment, to the possibility of repairing the brain and restoring lost function. The time has come when the brain is no longer just a place for research, it is a place for cures.

The NIH recognizes this shift and has taken some steps to respond. Unfortunately, vacant leadership positions have prevented the bold action we need. Our foundation has succeeded thus far mostly by tapping into the enormous backlog of promising, yet underfunded and unfunded science. We did not create this opportunity. We are simply responding to it with whatever resources we can muster. As exciting and gratifying as it is, seeing the possibility only increases our impatience and sense of frustration of what is not getting done. NIH has the resources and the infrastructure to do much more.

To meet the opportunity, I encourage the new NIH Director to immediately fill the open NINDS Director position and to do so with someone committed to using all available tools, including the Director's discretionary budget authority. I believe the NIH should responsibly pursue all available regenerative therapies for Parkinson's and other diseases and adopt an aggressive, proactive Bunsen burner to bedside approach to creating cures not just research.

I will shorten my comments.

PREPARED STATEMENT

In describing our efforts, we often make analogies to great achievements like the moon shot. But I am here to tell you that administering a successful research program is not rocket science. It is mostly common sense and the will to get things done. And we are going to get this done. This subcommittee, this Congress, and the NIH have the opportunity to make it happen in time for many more people today living with Parkinson's.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF MICHAEL J. FOX

Mr. Chairman, Senator Specter, and members of the Subcommittee, thank you for this opportunity to testify.

Is it just me, or were you sitting in different seats the last time I was here?

I apologize if that is a sore subject for some members of the Subcommittee, but I bring it up only to make the point that it is a tribute to you that irrespective of the musical chairs of electoral politics, and who sits in which seats on the dais, this Subcommittee's commitment to biomedical research funding remains constant.

Mr. Chairman, all Iowans, and indeed all Americans, should be grateful for your leadership on issues of health, including your continuing efforts to make biomedical research a higher nation priority. This Subcommittee—along with other individuals in this room—have spearheaded a historic effort that will soon succeed in doubling the budget for the National Institutes of Health over five years. You have accomplished this feat through difficult budget times, through changing administrations, and even through changes in majority control—an achievement that underscores the notion that illness and injury truly are non-partisan issues needing bipartisan solutions.

I am grateful for the Subcommittee's invitation, but I would not have come back again if I did not feel I have something constructive to add. None of us here has any interest in becoming another of this city's self-perpetuating cottage industries. Our appeals to you are part of our larger effort to accelerate the cure for Parkinson's disease. Much progress is being made, but there is no question that a well-funded and coordinated effort by the federal government would hasten the pace. And as you have already heard, time lost to Parkinson's inevitably means that lives are lost as well.

You've also heard from Dr. Isacson about the wide array of promising research opportunities relating to Parkinson's. He and dozens of other senior investigators make clear the inevitability of a breakthrough. Taken together, their message is unmistakable: curing Parkinson's is not a question of "if"? It is a question of "when"?

Back in 1999, I testified that Parkinson's research was far ahead of the money. Joan, Dr. Bill Langston, and I all testified that high quality and high-impact projects were being slowed down or stalled completely by the lack of available support. In addition to appealing to you and the NIH, we saw there was more we could do ourselves. With their help and advice, and together with a group of like-minded people, we launched a foundation with the single purpose of stimulating and supporting research, strategic thinking, and collaborations to accelerate the cure for Parkinson's.

We are lay people committed to enabling the work of scientists, and to do so we focus on the process of identifying, funding, and tracking research. We try to target where we can have the biggest impact and to employ the best methods to shorten the funding cycle, share the outcomes of research, and stimulate a coordinated effort toward the cure.

Some of our programs support investigator-initiated grants—the bread and butter of the NIH system and an indispensable mechanism for supporting new ideas—but in keeping with the higher-risk, higher-reward nature of our mission we've streamlined the NIH model and added our own wrinkles.

We've also enlisted scientists to identify the highest-priority areas of research and recommend proactive steps we can take to move the field forward in meaningful ways. Such assessments have lead to several specific funding initiatives, including the development of a cell line specifically for the study and treatment of Parkinson's.

One month after the meeting that made the recommendation we launched a $2.2 million initiative to develop cell lines with characteristics deemed relevant to Parkinson's. We received applications from a veritable who's who of cellular biologists worldwide. The number and quality of the proposals compelled us to double the program's budget to $4.4 million, which allowed us to support a portfolio of projects exploring all the promising techniques for creating cell lines from adult, fetal and embryonic cells. The number and diversity of these programs will allow for a meaningful comparison of these exciting technologies.

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Development of such promising new therapies puts us on the threshold of a new era of medicine. Today a good neurologist may be able to do little more than tell you the name of the disease that's taking away your life, or in some cases he or she may be able to give you a prescription or two to ease the symptoms for a few years. It's not a great proposition, but there is a paradigm shift underway. Understanding of the brain and of neurological disorders has advancing at a rapid pace, moving from definition of the disease to treatment to the possibility of repairing the brain and restore lost function.

Not too long ago it was an anathema to think that the brain has any capacity to regenerate and repair itself. But in recent year many scientists have embraced this recently revolutionary concept and run with it. Dr. Isacson, for example, is so convinced in the potential of the science that he has named his lab the "Neuroregeneration Laboratory."

NIH recognizes this shift and has taken some appropriate steps to respond. Nonetheless, they still trail behind the scientists out on the cutting edge—those whose experience increases our confidence that a cure is within reach. Our own experience shows the type of efficient funding process that is possible and the level of interest there is in doing the necessary work. All of this is tremendous progress, but it also increases impatience and sense of frustration over what is NOT getting done.

To meet the opportunity, I encourage the new NIH Director to fill open NINDS Director position, and to do so with someone committed to using all available tools—including the Director's discretionary budget authority—in the fiscal year 2002 and fiscal year 2003 budgets to direct significantly more funding toward implementation of PD Research Agenda. I believe the NIH should responsibly pursue all available regenerative therapies for Parkinson's and other diseases, and to adopt and an aggressive, proactive "Bunsen burner to bedside" approach to pursuing cures, not just research.

I want the Subcommittee to know that we in the private sector hope to engage in greater collaboration with NIH when tapping Parkinson's researchers for advisory and planning meetings. The goal is to reduce the number and replication of meetings and allow more time for the best scientists to work in their labs.

When I first appeared before this Subcommittee I spoke about my experience with Parkinson's disease. I did so in very personal terms because that is what I know. I know my own Parkinson's, which is different than Muhammad's, or Joan's, or Don's, or Milly Kondracke's. Every person who is diagnosed with Parkinson's is given their own custom version of the disease—and no operating instructions, I might add.

The other thing given to every person diagnosed—particularly the growing number of young-onset cases—is a reason to hope.

We are told that scientists are making great progress and that with the proper funding there may be a cure in five or ten years. We hear that there is no shortage of good ideas, just a shortage of research money. More recently we have been told that more money is on the way. The heroic efforts of the grassroots advocacy community are having an impact and Congress is taking steps to ensure more Parkinson's research funding. Congress passed Parkinson's-specific legislation, asked NIH to develop a Parkinson's Research Agenda, and last year adopted strong report language urging more funding and full implementation of the research agenda.

These have each been significant accomplishments, and we are all grateful to this Subcommittee and your colleagues in the Senate and House for your support. And yet despite these legislative achievements, support of Parkinson's research has failed to keep pace with the overall growth in NIH's budget, it has not meet the goals of the NIH Research Agenda and it falls far short of the scientific opportunity. Is it that this system is not designed to systematically and aggressively study, treat, and cure a disease? If that's true, we have got to reinvent the system.

NIH has a vital roll funding basic research and supporting scientific explorations. But when there are opportunities to reduce human suffering and societal costs by curing a disease like Parkinson's, then I think it is appropriate for the National Institutes of Health to commit a fraction of it's resources to actually treating the nation's health. Parkinson's disease is both an individual and national challenge. We

ought to act as surely as we act in response to other challenges to our health, our lives, and our society.

I would not take this coveted time before the Subcommittee to argue for something than cannot be done. Our experience is evidence that it can. And we'll keep at it, because unlike some other reports you may have heard, we have yet to determine any shortage of interest in Parkinson's research or in high-quality, high-impact projects that await funding. Don't let anyone tell you that everything that can be done is being done or that the scientific community has reached its capacity for Parkinson's research.

What's more, I believe we are at the "tipping point", the moment of critical mass when the momentum towards the cure becomes irresistible and the only remaining question is whether the federal government will be helping lead the process, or will it be trailing along behind?

In describing our efforts we often make analogies to great achievements like the moon shot. But I am here to tell you that administering a successful research program is not rocket science. It is mostly common sense and the will to get things done. And we're going to get this done. This Subcommittee, the Congress, and the NIH have the opportunity to make it happen in time for many more people living today with Parkinson's.

Thank you.

Senator HARKIN. Michael, that was a very profound statement. Thank you so much.

Before I turn to Senator Specter, who would like to ask some questions and make a statement, we have now been joined also by another former U.S. Senator and former Secretary of Transportation in the administration of President Carter. Our former colleague, Senator Brock Adams of the State of Washington, is also here.

Senator Specter.

Senator SPECTER. Thank you very much, Mr. Chairman, for deferring to me. I am going to have to excuse myself in a few moments and wanted a chance to make a few closing comments.

This is an unusual hearing where there is applause. Customarily there is tough cross examination on witnesses when we have to get into some of the very difficult matters. But there is a lot of love in this room and a lot of unity of purpose to try to reach a common goal, and that ought to be noted.

This subcommittee will pursue these issues with great intensity, as we have, and we will try to see to it that there is full funding for Parkinson's, because it is true that the money is there. The funding is there and it is a matter of allocation. We try to depoliticize the matter by leaving it to the discretion to the National Institutes of Health, but we have a view and they do listen to us more than occasionally.

Dr. Ruth Kirschstein is smiling. She had been acting Director of NIH and she is now Deputy Director. I join Senator Harkin in saluting you, Dr. Kirschstein, for your great service and the award which you have received today.

I compliment you, Mr. Fox, on many things, but you noticed the role reversal up here. Senator Harkin has the gavel. I touch it. It is almost too hot to handle.

Senator Harkin had been the chairman back in 1994 and I took over in 1995 for 6½ years. But we have had a seamless transition. It does not make any difference between Tom Harkin and Arlen Specter who the chairman is. I think we both learned a long time ago, if you want to get something done in Washington, you have to cross party lines. I know the American people are sick and tired of the bickering that occurs in Washington, which is all too fre-

quent, but not on this subcommittee and not on this purpose. And we are determined to move ahead.

Joan Samuelson, I know exactly what you mean with your comment about no time to lose. I think that is exactly right. You only have your health once, and there is no time to lose. A constituent of mine, Jim Cordy, in Pittsburgh, who suffers from Parkinson's carries around an hourglass, and whenever he sees me, he inverts it to let me know that the sands of time and the seconds of his life are ticking away. That is the kind of intensity which we appreciate and understand.

Mr. Don Schneider, you have still got a strong voice. You can tell radio there. You can tell projection. We hear you. We hear you loud and clear.

And thank you, Dr. Penn and Dr. Isacson, for what you have contributed here today.

Muhammad Ali was in Pittsburgh not too long ago. He has great resiliency in responding to the bell to come out swinging, and with The Champ in our corner and with Mrs. Lonnie Ali's eloquent statement, we have our work cut out for us.

We have special momentum from Claiborne Pell, Mac Mathias, Brock Adams, and Mrs. Russell Long, and really from millions and millions of Americans.

I would conclude on the note which Michael J. Fox sounded about the pending legislation. Everyone in America is either afflicted with the disease, has a family member afflicted with the disease or knows somebody who is. If there is an understanding that this legislation could cripple the efforts to use stem cells to cure Parkinson's, Alzheimer's, heart disease, and cancer, et cetera, America would rise up in an avalanche. That is a message we are working to carry forward. This hearing is very, very helpful because of the focus of attention it has brought on this critical problem.

So, I thank you and I give you the pledge of the subcommittee—I know I speak for Tom Harkin and all the members—that we will continue fighting, and I think we are going to win it. Thank you all very much.

Senator HARKIN. And though not a member of the committee, but again, one of the most effective and powerful voices in fighting Parkinson's in the entire United States Congress, Senator Paul Wellstone.

Senator WELLSTONE. Thank you, Tom.

You know, Arlen, I do not know that we always agree, but I cannot think of a word that you just uttered that I could disagree with. And I just would like to say to everybody here, those who testified, those who came, everyone, and all the people that your represent around the country, it is an absolute honor to work with you. We will all take this journey together, and there is no doubt in my mind that we will succeed. Thank you.

Senator HARKIN. Thank you very much, Paul.

Well, since they just both gave my speeches, I will just refrain from giving a speech here. But I would like to ask a couple of questions, make a point, and then maybe ask a couple of questions.

Dr. Penn, I know that you put that chart up that pointed out the increases in Parkinson's disease funding in the mid-1960's that was above the annual increases at NIH.

Dr. PENN. Sir, it is 1996 to 2001.

Senator HARKIN. 1996, 1997, 1998, 1999, and 2000.

Dr. PENN. Right, over 5 years.

Senator HARKIN. For argumentative purposes and debate purposes, we can all use percentages to try to make our case. When people tell me that we have had this huge percentage increase in anything, I always ask one question. What is the baseline? You see, to go from 0 to 1 is an infinite percentage increase. So, I have got to know what the baseline is. Quite frankly, yes, I would agree that percentages were higher, but we started from a very, very low baseline.

So, I think what we have to look at in cases like this, especially in biomedical and medical research, is where are you in the spectrum from knowing nothing to translating it into a cure. Where are you on that?

It would seem to me that in this specific case of Parkinson's, that needle is way past the halfway mark in terms of knowing nothing, starting the basic research, to getting to the point of doing translational types of applications. Now, that is the point at which we have to focus not so much on percentages and percentage increases, but what are the requests out there for projects, what are we capable of doing in translating this research to the bedside, what are we capable of doing right now in moving ahead from the basic research, which we have passed a lot by—Dr. Isacson spoke about it—to really translating this into clinical trials?

So, I am not interested in the percentage. I want to know how much money overall will it take to move that needle towards the cure from where we are right now. And that is what we are focused on here. What is it going to take dollar-wise, not percentage-wise?

Now, I know the President's budget has $215.1 million for Parkinson's funding for next year. That is up from $198.8 million from last year. That percent would be 8.2 percent. But again, I would like to get off the percent increase. I want to know what is it going to take dollar-wise. I do not know if you could speak to that or not, Dr. Penn.

Dr. PENN. I couldn't possibly estimate dollar-wise. What I can say is that at NINDS, and with the rest of the institutes, we are convinced that the scientific advances have been really excellent, that all the investigators that came and participated and were involved in the Parkinson's Research Agenda that have put in applications that went successfully through rigorous peer review have been funded. We funded 80 applications in 2 years between 2000 and 2002 on——

Senator HARKIN. 80 percent?

Dr. PENN. 80 brand new applications. The average cost of these at this point is about $400,000. We have got the initiatives out there. We are funding the Udall centers. And when we had the meeting of the consortium in January of 2002 to look again at this agenda and where we were going, the investigators did not want to talk budget. They wanted to talk science, and they were very pleased at the fact that all the areas of the agenda were really

moving forward. So, as I tried to say in my opening statement, I think we are on the verge of excellent control and a much better quality of life, though we are going to need to work on all of the things that Dr. Isacson mentioned to achieve a cure.

Senator HARKIN. Well, the Parkinson's Research Agenda is intended to answer the dollar question. I might turn to Joan on this and just ask you. The Parkinson's Research Agenda is asking for, as Mrs. Ali mentioned, $353.3 million. Again, I do not need you to go into great detail, but how do you arrive at a figure like that?

Ms. SAMUELSON. Well, the scientists did it. They met and discussed several areas of research with great promise in detail. They had the experts from all the areas. And they put dollar amounts on it. It is interesting, because we had a research plan just sponsored by the Parkinson's Action Network before the NIH's, and it arrived at similar numbers. It was a matter of the scientists who are the best in the field, who understand what it takes to run the lab and to do the work and have the wish list of projects that they are not funding, devoting their time to figuring it out. That is the same thing that happened with the NIH's. It was a very deliberate, elaborate process with a room full of investigators who are NIH recipients and understand the process. It was a very sober, careful process that arrived at these numbers that would gradually add up to an increase of $1 billion over 5 years.

Senator HARKIN. So, from that, you are saying that there is enough in the scientific community to warrant that kind of spending that would be solid, good research, and I assume some trials within that.

Ms. SAMUELSON. Absolutely.

Senator HARKIN. Dr. Penn, will we be doing some trials in the next year?

Dr. PENN. Yes, we will and we have the agents. The meeting was yesterday on the neuroprotective agents that are potentially useful. Of course, they have to be studied in pilot trials before you put them safely into phase III trials on humans.

We also are doing this trial with the Veterans Administration on the deep brain stimulation which I think will really improve control enormously. It also has the potential of improving the motor side effects of L-dopa, and that would be tremendous because L-dopa is a wonderful drug. It just causes all kinds of side effects.

We have got to replace the cells, though. I will not deny that.

Senator HARKIN. Well, that leads us to Dr. Isacson then. Two things I want to ask you about. I understand that your center is investigating a number of different neurological disorders, Alzheimer's, Huntington's, ALS, Parkinson's. There may be others that I do not know about. Which of those do you believe is closest to actually having some form of a cure?

Dr. ISACSON. Oh, I think it is absolutely Parkinson's disease. The understanding of the underlying disease process is clearer in that case and also probably the treatments are going to be simpler in the sense that once you have the science.

You need, however, to build capacity here in the sense that the Parkinson's Research Agenda that was mentioned—that is a scientific document that has been evaluated in terms of what you would need in terms of funding. But to implement that requires an

effort. It requires innovation also in the way that the centers are organized. We talk now about core facilities to build up services for the scientific labs to move faster. There is a need to build capacity into the system. Even when you have made a scientific discovery, you need to move it forward.

I feel that the scientists and clinicians involved in this effort need to work with NIH. We seem to have a good understanding and agreement on the pieces here, but your leadership on this issue and pointing out that we need to take a very aggressive path forward that we understand is a reasonable thing to do.

Senator HARKIN. Dr. Isacson, I understand also that by moving ahead aggressively in Parkinson's—it is my understanding at least from your testimony and others'—that may lead to other avenues of cures for other neurological disorders.

Dr. ISACSON. If I may comment.

Senator HARKIN. Yes, please.

Dr. ISACSON. I am glad you asked that. I am convinced that when we talk about treatment modalities, most of us know we can go to the pharmacy and we get a drug. But there are new modalities that will come out of what we have discovered and worked on in the States for a long time, for example, the genome project. All these knowledge bases in science are likely to generate new technologies, new modalities. And when we break open the door to new treatments for Parkinson's disease, there is going to be a lot of movement also for other diseases, and I am thinking about ALS, Huntington's disease, even spinal cord damage. So, I can assure you that the scientific community again agrees on this, that it is useful and reasonable to spearhead Parkinson's disease, to open up the new treatment modalities.

Senator HARKIN. I understand that you have had some notable success—and you mentioned it—in using embryonic stem cells in rats that were undifferentiated that you put into the brains of rats. You had instilled in them the Parkinson's-like disease and these rats have recovered. Is that so?

Dr. ISACSON. That is correct.

Senator HARKIN. Is it not so that we are about 95 percent like a rat?

I do not mean we politicians. I am not saying that.

I am saying we as humans, I think genetically. The genes. Do we not share about 90-some percent? I do not know what it is, but it is pretty close.

Dr. ISACSON. Just to be contradictory, I think that none of the psychology seems to overlap.

But biologically speaking, you are right.

Senator HARKIN. Genetically speaking.

Dr. ISACSON. Genetically speaking, there is a huge overlap. What we learn from animals—we call them animal models—we can usually create models for new therapies. One can call them prototypes to have a more general understanding. And those prototypes that we build, sometimes even in fruit flies, give us knowledge and insight about molecular mechanisms and what I call the new therapeutic modalities, new technologies to help the patients.

So, yes, the kind of work we have done on stem cells is important. It is very clear that we can obtain the cells that die in Parkin-

son's through stem cell work, and as I mentioned previously, I think it is absolutely necessary to have freedom of research typical of our country to pursue that vigorously as you have indicated in your bill, for example, on nuclear transplantation.

Senator HARKIN. Give me some idea. When do you think we would actually—I mean, looking ahead, if we had a robust increase in Parkinson's funding for the next year, take me down the road a little bit. I can ask Dr. Penn this or maybe even Joan. I will ask anyone. When do you think we might actually see some human clinical trials?

Dr. ISACSON. Well, my opinion, in this case, of course, is an opinion.

Senator HARKIN. That is all I am asking.

Dr. ISACSON. My thinking on this is that we are very close. There are a number of these research areas, defined in this Parkinson's Research Agenda by NIH, that are likely to generate clinical trials. As mentioned by Dr. Penn, neuroprotective trials for up to $500 million over the next 7 years will give us insight about new drugs that can prevent the cells from dying. We are looking also at gene therapy, sometimes misunderstood, but again, taking advantage of the molecular revolution, genome project, to look at new drugs that use therapeutic genes. That is likely to move into pilot clinical trials quite soon, maybe before 5 years.

So, to give you an impression, I think a number of these efforts are moving along, as you said I think correctly, in the process towards what is reasonable. I always say that FDA is sometimes lambasted for not being responsive, but in the end we come there with our ideas and they look at them if they are safe, and then we test them. But there is a process there.

Senator HARKIN. Dr. Penn, anything else on that?

Dr. PENN. I would say that FDA is actually a partner. We have talked to them about how we would move when using the approved ES cell lines in people because, after all, there are several issues there. So, they are waiting in the wings for us to get to that point.

I have talked to our own major investigator in this area who is in our intramural program who is proceeding to, as I said in the statement, drive the human ES cells toward dopamine cells. He thinks that will take him 1 to 2 years to just do it, and then, of course, you have to get it into the brain safely and you have to fulfill the FDA guidelines. And then we could actually get to a pilot clinical trial in people.

But again, science moves up and then it moves back, and you cannot always predict. So, I do not want to give you an exact date. But we fully intend to move into clinical trials with the approved cell lines as soon as we can.

Senator HARKIN. That brings me to Michael Fox then. What you have been doing with your foundation on the fast track funding process that your foundation has worked out with NINDS, can you tell us just again, Michael, how this works and what you have been able to do so far?

Mr. FOX. To sum it up, basically we approach this problem—and one of the reasons why I went through the things that we had done was not so much to blow our horn, but to show that what this really calls for I think—our proximity to the goal calls for really an in-

novative approach and to know that if we had—just, for example, the amount of time that it takes for an application for a grant, if we can trim those processes in a responsible way, if we can make it easier for the scientists to do what they need to do and just take an innovative approach to the way the machinery of science normally works, we can hasten our march toward a cure.

So, what we were able to do was to cut down. We put out an RFA, request for application, for our first round of grants. I believe that the time frame was something like 3 months, much shorter. What happens then is you attract a lot of different researchers that might not have been able to do it otherwise and you widen the field of people who want to get involved and then you widen the talent pool.

What had happened in our case was we were very fortunate to have the NIH come to us and comment on that fast track and join us and help us fund some of those proposals. So, it was a very exciting response from them and very responsible, and we were thrilled. For us, it really showed that there can be innovative partnerships and goal-oriented partnerships that make it easier for scientists to do the work.

There is nothing harder for a scientist than to initiate a field of study and then have funding dropped out or to not know what they are getting into. It is not a question sometimes of a scientist not wanting to do the work or not having work to do, but he is a person too and he or she has responsibilities to their employees and to the lab and to their families. So, they need to know that they will be backed all the way and that things will be made to facilitate their work. These are not wizards in the sky. These are people doing real work. So, we need to appreciate that and make it easier for them.

Senator HARKIN. Dr. Penn, how do you feel the partnership is working?

Dr. PENN. The partnership is working. We were very fortunate to be able to partner with the Michael J. Fox Foundation.

And just for the record, the reviews for those innovative fast track grants actually occurred on September 11, and people finished the reviews because it was so important and did not try to—they could not leave town. We could not even get back to NIH. But it was accomplished. We have a great group.

We have always worked with voluntary organizations to identify new and promising investigators, and to try to start up research, because those folks do have to go through peer review ultimately for their next grants, and we like to make it as straightforward and as promising for them as possible.

Senator HARKIN. Again, congratulations on the foundation and what you are doing with this partnership is very innovative. It is something I have not seen before.

Mr. FOX. Thank you. That is what we need, though.

Senator HARKIN. We might use the model for other things too, you know.

Mr. FOX. I did not have a chance to say it early but everybody on this panel I thank personally for the things that they have done. I think a lot of people bring innovative thinking to this problem but the problems are so real and the need is so real and the urgency is real. And we really feel we can get this done.

Senator HARKIN. Don Schneider, I have a couple of questions, but one I really have got to ask you. What year is that red Corvette?

Mr. SCHNEIDER. 1977.

Senator HARKIN. Is that right? I had a 1977 Corvette. Well, we cannot take this time to talk about Corvettes.

Mr. SCHNEIDER. I can dust it for fingerprints.

Senator HARKIN. We will do it later sometime.

As somebody who has been very active all his life and taken charge and everything, it would be helpful for you to put a human face on things, just talk a little bit. What did you have to do to get ready for this morning?

Mr. SCHNEIDER. When I get up in the morning, I cannot walk. My feet shuffle like they are stuck to the floor. I tremor, shake the whole bed, until my medications kick in. Then once my medications kick in, it is just like a light switch. I go from not being able to move to being able to do anything. That lasts for a couple hours, and then the next dose is due. That is my day.

Senator HARKIN. Mrs. Ali, how about you and how about Muhammad? How is his day?

Ms. ALI. Yes, Muhammad has been quite fortunate because he was diagnosed with Parkinson's in 1981, so he has had it for over 20 years and probably had it before then. But I have seen the progression in the last 5 or 6 years similar to what everyone here has related. And Parkinson's is like every other disease. It is individual. It affects people in different ways.

If you ever looked at a fight tape of Muhammad or an interview or a documentary, you know how he lit up the screen and how he loved the camera. Now you see him sitting here with his eyes closed. It is not because he is trying to block you out, it is because Parkinson's made him photophobic to light. His face does not love the camera like it used to.

In fact, I think the biggest thing that Parkinson's has done is rob this man of his confidence which I think is just absolutely horrible. I think we are being deprived of a lot of things from this man and a lot of other people, but his day is not like it used to be. It is very difficult for him to move around. He is a prisoner in his body.

Senator HARKIN. Of all the good that you have done, Muhammad, around the globe, I still believe that you are one of the greatest ambassadors of good will this country has ever had. If I were President, I would be calling on you, I can tell you that, even with Parkinson's. I think again the courage that you show to people around the world who know you, this could have a profound effect and will have a profound effect on people. There are a lot of people around the globe who look upon you, and rightfully so, as a great hero of theirs. They may not have much hope for their lives, but you give them hope. So, I encourage you, Muhammad, keep on and just keep on fighting. You got it, man.

Well, Mrs. Ali, you quoted Dr. William Langston who said sometimes you hit the point where it is time to focus.

Ms. ALI. That is correct.

Senator HARKIN. And now is the time to focus.

I thank you all for being here. I will close by just saying that, first, a disclaimer. We do not on this committee specify what NIH has to do. We are not scientists. I am not a scientist. I believe over

my years here, though, I have absorbed quite a bit. I am not an expert, though. But I have been on this committee now 18 years, first under Lowell Weicker and then Lawton Chiles. Then I was chairman, then Senator Specter, and now I am back again as chair. Through those years, we have seen great progress made through NIH. It really is the crown jewel of the Federal Government, no doubt in my mind. And I am proud that Senator Specter and I were able to work together collaboratively to double the funding for NIH. So, I do not feel within my purview or Senator Specter's or anyone else to tell NIH put this money in this research, put this money in that research.

But I am a public servant. I have to reflect what the public wants. That is my oath of office. I also need to translate to NIH what we hear here in this hearing room. Now, scientists are doing their job. Our job is to try to help them do their job, not in the way of explicitly telling them what to do, but our telling them here is what we are hearing from the public. Here is what we know on the record. Here is what experts from different fields have told us. And it is the interest of this subcommittee that funds NIH that you take this into consideration and look at it in your decisions on how much to put in funding different disease groups.

That is why last year some people say I stepped out of bounds—but I do not believe so—in the language that I inserted in with our funding bill on Parkinson's. Year after year, under Senator Specter and last year under my chairmanship, we kept seeing that needle move more and more away from just the basics into actually something that needs to be translated. So, we wanted and I wanted specifically to put some very strong language in there not just to tell scientists what to do but to tell them here is the sum and substance of what we have heard here, not just me, but all the witnesses, the experts, the other scientists in the field are saying. And you need to act on this and come back and tell us what you are going to do.

So, I think that is a proper role for us to play here and we will continue to play that role. So, I will in drafting the language on this bill again say to Dr. Zerhouni, who is now the new head of NIH, that this is what we are hearing, that the language I used last year was intended to let you know that this committee feels very strongly that we need not just a percentage increase, but we need to get as close as possible to the research agenda put forward by the Parkinson's Action Network. As close as possible.

And you have my word that language will be in there this year.

In our oversight hearings, we will have again Dr. Penn and the head of NIH down to ask what they are doing in this area, because I believe this is what this committee has heard from you and from other witnesses, that we need to move ahead aggressively in this area.

So, again, I thank you all very much for being here. Joan, I think thank you especially for your great leadership in this area. You have been the driving force behind this. Actually, you know, Joan Samuelson probably wears about a 5 shoe or 6 shoe, but I feel sometimes it is about a size 15 in the middle of my back sometimes.

But it feels good because you are doing the right thing and you keep us informed and advised. You keep pushing us. And that is what you ought to be doing too. Keep on pushing us too.

Dr. Penn, thank you for your leadership there.

Muhammad Ali, Michael J. Fox, thank you so much for your leadership, your inspiration. You have given us all this hope and courage.

Don Schneider, see you back in Clinton. We are going to lick this thing.

PREPARED STATEMENT AND LETTER RECEIVED

We have received the prepared statement of Senator Thad Cochran and a letter from Do No Harm: The Coalition of Americans for Research Ethics. They will be placed in the hearing record.

[The statement and letter follow:]

PREPARED STATEMENT OF SENATOR THAD COCHRAN

Mr. Chairman, thank you for conducting this hearing on Parkinson's Disease research. Parkinson's Disease is a good example of how our efforts to increase medical research funding are making a difference.

We began this effort in 1997 with the Morris K. Udall Parkinson's Disease Research Act. Since that time, there has been impressive progress in the effort to find a cure.

Important areas of this research include prevention, diagnosis and treatment of Parkinson's. Another important development has been the collaboration between NIH Institutes and researchers. We must explore further how advances in imaging technologies can improve diagnosis and treatment of Parkinson's. We must also consider such areas as the link between environmental conditions and the disease. We can only address many of these issues through greater NIH research collaboration.

I agree with a statement Michael J. Fox made several years ago that "this is a winnable war". I believe, however, it is only winnable if we continue our investment in research. I thank the researchers and patients here today for keeping us focused on how this investment will help us win this war.

LETTER FROM DO NO HARM: THE COALITION OF AMERICANS FOR RESEARCH ETHICS,
MAY 21, 2002.

Hon. TOM HARKIN,
Chairman, Subcommittee for Labor, HHS and Education,
Senate Appropriations Committee, Washington, DC.

DEAR SENATOR HARKIN: I would like to submit this letter and enclosed fact sheet as a written submission for your May 22 hearing on Parkinson's disease. These are submitted on behalf of Do No Harm: The Coalition of Americans for Research Ethics, a coalition of scientists, researchers, bioethicists and others supporting adult stem cell and other research avenues to cure disease that do not rely on the creation and destruction of human life.

It is important to note how predictions have changed in less than a year regarding the most promising avenues for Parkinson's research.

Last summer the Parkinson's Action Network urged Congress to support federal funding of embryonic stem cell research, declaring: "We need a medical rescue and we need it now. Scientists agree it is possible this decade" (PAN press release, July 17, 2001). Just a few months later, however, PAN testified to the President's Council on Bioethics that clinical benefits from this source are highly uncertain—and that any benefits which do ultimately arrive may take "another generation" to help human patients (Statement of Elisabeth Breese Brittin, Transcript of the President's Council on Bioethics, January 18, 2002). This shift in prognosis is warranted by the very disappointing results thus far from the use of embryonic stem cells. These cells have produced some modest benefits in animal trials for Parkinson's disease, but also shown a disturbing tendency to form lethal tumors when placed in living animals. Thus they are a very long way from being considered safe (let alone effective) for human clinical trials. Use of stem cells from cloned embryos poses its

own additional problems and risks, due to the havoc wreaked by the cloning process upon orderly gene expression and other factors.

Fortunately, there is also great reason for hope regarding this disease. At the same time that timetables have been lengthened for benefits from embryonic stem cells, timetables have been moved up for benefits from adult stem cells and other alternatives. Recent clinical trials have shown an almost complete reversal of Parkinson's symptoms for one patient, using his own adult stem cells, and very promising results for several other patients using donated adult retinal cells. These avenues, as well as new advances in gene therapy and other approaches, do provide reason to hope that we can indeed speak of a cure for Parkinson's in this decade.

We hope Congress will take note of these new developments, which provide a "win-win" situation for all involved in the stem cell debate: A clear path to new treatments and perhaps cures, without posing the moral and legal problems connected with embryo research and cloning.

Sincerely,

GENE TARNE,
Communications Director.

TREATING PARKINSON'S WITH ADULT STEMS CELL AND OTHER ALTERNATIVES

IN HUMANS

Total Reversal of Symptoms Reported

Using adult neural stem cells, Dr. Michel Levesque, at the Cedars-Sinai Medical Center in Los Angeles, reports a total reversal of symptoms in the first Parkinson's patient treated. The patient, a 57-year old former fighter pilot, is still without symptoms three years after the adult neural stem cells were removed from his brain, coaxed into becoming dopamine-producing cells, and then reimplanted. Because the stem cells came from the patient, there was no need for immunosuppression to overcome rejection. "I think transplantation of the patient's own neural stem cells and differentiated dopaminergic neurons is more biologically and physiologically compatible—more efficacious and more elegant," said Levesque. In addition to its use for Parkinson's, the technique is under study for juvenile diabetes, stroke, brain tumors, spinal cord injury, and other conditions.

Reference.—Results presented April 8th, at the meeting of the American Association of Neurological Surgeons.

Retinal Cell Implants Improve Parkinson's

A team at Emory University School of Medicine has shown that implanting retinal cells into the brains of people with advanced Parkinson's disease can improve motor function by almost half, according to a follow-up study of six patients. The team noted: "We've been following these six participants for over a year, and we've found they've improved, on average, nearly 50 per cent in motor function." The retinal cells used were taken from deceased donors and grown in the lab. The team is not using immunosuppressants.

Reference.—Result presented April 18 at the annual conference of the American Academy of Neurology in Denver and reported in the *New Scientist*, 18 April 2002.

N.B.—There are no clinical treatments for Parkinson's based on cloning or embryonic stem cells.

IN ANIMALS

Stimulating Adult Brain Stem Cells Decreases Parkinson's Symptoms

Injection of growth protein into brains of Parkinson's rats caused their neural stem cells to grow, migrate to the site of damage, and begin to replace missing nerve cells. Eighty percent (80 percent) of the rats received a benefit from the treatment, with no tumor formation.

Reference.—J. Fallon *et al*.; "In vivo induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain," *Proc. Natl. Acad. Sci.* USA 97, 14686–14691; December 19, 2000.

Progenitor Cells Reverse Severe Parkinson's Symptoms in Rats

Researchers at Chicago's Rush University report coaxing progenitor cells from the brains of rats into becoming dopamine neurons to treat Parkinson's disease. Led by Paul Carvey, the team discovered an important "shortcut" to creating a more efficient, more reliable, and safer source of stem cells with the ability to turn into specific neurons or brain cells. This study is the first to identify the signal that instructs stem/progenitor cells to become dopamine neurons. The researchers watched the cells develop, and selected and grew cells that were close to becoming neurons.

They then grafted the cells into brains of Parkinson's rats, effectively curing the animals' severe Parkinson symptoms. The ability to select and grow large numbers of adult stem cells that would become neurons also has the potential to revolutionize the treatment of Alzheimer's disease, multiple sclerosis and numerous other diseases and disorders of the brain and nervous system.

Reference.—Results reported at the Experimental Biology Meeting in New Orleans, April 2002.

N.B.—In contrast to these animal studies using adult stem cells, a widely publicized study showed Parkinson's rats injected with mouse embryonic stem cells receiving a modest benefit for just over 50 percent of the rats, but one-fifth (20 percent) of the rats died of brain tumors caused by the embryonic stem cells.

Reference.—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; Feb 19, 2002 (published online Jan 8, 2002)

Gene Therapies Treat Parkinson's in Rats, Monkeys

The injection of two corrective genes into a specific brain region generated significant restoration of normal limb movement in rats with Parkinson's disease. Limb impairments were completely reversed in rats that had near-total Parkinsonian lesions on only one side of the brain, meaning that some of their dopamine-producing cells remained intact. But even in the rats with complete destruction of dopamine-producing cells, the delivery of gene therapy resulted in a limited amount of restored motor function. "We anticipate gene therapy will offer a way to help patients with Parkinson's disease live many years longer free of disabling symptoms," the researchers noted.

Reference.—D. Kirik *et al.*; "Reversal of motor impairments in parkinsonian rats by continuous intrastriatal delivery of L-dopa using rAAV-mediated gene transfer," *Proceedings of the National Academy of Sciences USA 99*, 4708–4713; April 2, 2002.

A Japanese research team has demonstrated delayed delivery of gene therapy can provide significant recovery from Parkinson's symptoms. Four weeks after inducing Parkinson's damage in their brains, rats were given an injection of a gene vector which produced a growth protein call "glial cell line-derived neurotrophic factor" (GDNF). The animals showed remarkably higher levels of dopamine secretion and significant behavioral recovery, even up to 20 weeks following the injection.

Reference.— Wang L. *et al.*; "Delayed delivery of AAV-GDNF prevents nigral neurodegeneration and promotes functional recovery in a rat model of Parkinson's disease," *Gene Therapy* 9, 381–389; March 2002.

Treatment with three gene therapy vectors has shown behavioral recovery in Parkinson's monkeys. The treatment resulted in remarkable improvement in manual dexterity and restoration of motor functions, with the behavioral recovery persisting for over 10 months in one case. The scientists say that this triple gene therapy method may offer a potential therapeutic strategy for Parkinson's disease.

Reference.—S. Muramatsu S. *et al.*, "Behavioral recovery in a primate model of Parkinson's disease by triple transduction of striatal cells with adeno-associated viral vectors expressing dopamine-synthesizing enzymes," *Human Gene Therapy* 13, 345–354; February 10, 2002.

CONCLUSION OF HEARING

Senator HARKIN. Thank you all very much for being here, that concludes our hearing.

[Whereupon, at 11:23 a.m., Wednesday, May 22, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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