FROM MOLECULES TO MINDS: THE FUTURE OF NEUROSCIENCE RESEARCH AND DEVELOPMENT

HEARING

BEFORE THE

SUBCOMMITTEE ON DOMESTIC POLICY

OF THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED ELEVENTH CONGRESS

SECOND SESSION

SEPTEMBER 29, 2010

Serial No. 111–159

Printed for the use of the Committee on Oversight and Government Reform

Available via the World Wide Web: http://www.fdsys.gov
http://www.oversight.house.gov

U.S. GOVERNMENT PRINTING OFFICE

65–562 PDF WASHINGTON : 2011

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

EDOLPHUS TOWNS, New York, *Chairman*

PAUL E. KANJORSKI, Pennsylvania
CAROLYN B. MALONEY, New York
ELIJAH E. CUMMINGS, Maryland
DENNIS J. KUCINICH, Ohio
JOHN F. TIERNEY, Massachusetts
WM. LACY CLAY, Missouri
DIANE E. WATSON, California
STEPHEN F. LYNCH, Massachusetts
JIM COOPER, Tennessee
GERALD E. CONNOLLY, Virginia
MIKE QUIGLEY, Illinois
MARCY KAPTUR, Ohio
ELEANOR HOLMES NORTON, District of Columbia
PATRICK J. KENNEDY, Rhode Island
DANNY K. DAVIS, Illinois
CHRIS VAN HOLLEN, Maryland
HENRY CUELLAR, Texas
PAUL W. HODES, New Hampshire
CHRISTOPHER S. MURPHY, Connecticut
PETER WELCH, Vermont
BILL FOSTER, Illinois
JACKIE SPEIER, California
STEVE DRIEHAUS, Ohio
JUDY CHU, California

DARRELL E. ISSA, California
DAN BURTON, Indiana
JOHN L. MICA, Florida
JOHN J. DUNCAN, JR., Tennessee
MICHAEL R. TURNER, Ohio
LYNN A. WESTMORELAND, Georgia
PATRICK T. McHENRY, North Carolina
BRIAN P. BILBRAY, California
JIM JORDAN, Ohio
JEFF FLAKE, Arizona
JEFF FORTENBERRY, Nebraska
JASON CHAFFETZ, Utah
AARON SCHOCK, Illinois
BLAINE LUETKEMEYER, Missouri
ANH "JOSEPH" CAO, Louisiana
BILL SHUSTER, Pennsylvania

RON STROMAN, *Staff Director*
MICHAEL MCCARTHY, *Deputy Staff Director*
CARLA HULTBERG, *Chief Clerk*
LARRY BRADY, *Minority Staff Director*

SUBCOMMITTEE ON DOMESTIC POLICY

DENNIS J. KUCINICH, Ohio, *Chairman*

ELIJAH E. CUMMINGS, Maryland
JOHN F. TIERNEY, Massachusetts
DIANE E. WATSON, California
JIM COOPER, Tennessee
PATRICK J. KENNEDY, Rhode Island
PETER WELCH, Vermont
BILL FOSTER, Illinois
MARCY KAPTUR, Ohio

JIM JORDAN, Ohio
DAN BURTON, Indiana
MICHAEL R. TURNER, Ohio
JEFF FORTENBERRY, Nebraska
AARON SCHOCK, Illinois

JARON R. BOURKE, *Staff Director*

CONTENTS

FROM MOLECULES TO MINDS: THE FUTURE OF NEUROSCIENCE RESEARCH AND DEVELOPMENT

WEDNESDAY, SEPTEMBER 29, 2010

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON DOMESTIC POLICY,
COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM,
Washington, DC.

The subcommittee met, pursuant to notice, at 2 p.m. in room 2203, Rayburn House Office Building, Hon. Dennis Kucinich (chairman of the subcommittee) presiding.

Present: Representatives Kucinich, Kennedy, Foster, and Jordan.

Also present: Representatives Thompson and Jones.

Staff present: Claire Coleman, counsel; Justin Baker, clerk/policy analyst; and Molly Boyl, minority professional staff member.

Mr. KUCINICH. Good afternoon. The Domestic Policy Subcommittee of the Oversight and Government Reform Committee will now come to order.

This hearing will explore efforts to expand knowledge and treatments to help individuals afflicted with neurological and mental health disorders. Without objection, the Chair and ranking minority member will have 5 minutes to make opening statements, prior to opening statements not to exceed 3 minutes by any other Member who seeks recognition.

Without objection, Members and witnesses may have 5 legislative days to submit a written statement or extraneous materials for the record. And without objection, for the purposes of participation in today's hearing, we welcome Congressman Mike Thompson to the subcommittee.

Today's hearing will address the critical needs for better treatment for neurologic and psychiatric disorders, and how the neuroscience community can best facilitate research to advance and accelerate discovery of treatments and cures. Every year, the more than 1,000 disorders of the brain and nervous system result in more hospitalizations than any other disease group, even more than heart disease and cancer. Neurological illnesses affect more than 50 million Americans annually at costs exceeding $460 billion.

Neuropsychiatric illnesses, like schizophrenia, mood disorders and autism are the leading cause of disability in North America and Europe. In the United States, the cost in lost earnings due to psychiatric disease is estimated conservatively to be $200 billion per year. The toll of brain-related disorders is enormous for individuals and for families. Veterans returning from wars in Iraq and Af-

ghanistan have been particularly hard hit by neurologic disorders. Traumatic brain injury, defined as a disruption in brain function as caused by head injury, has become known as one of the signature wounds of the wars in Iraq and Afghanistan, because of the insurgents' heavy use of explosive devices and armor which has better protected soldiers' lives from life-threatening injuries. That is despite the fact that we have better-protected soldiers.

A disproportionately high number of returning military personnel also struggle with psychological health issues like post-traumatic stress disorder, clinical depression, anxiety disorder, sleep disturbances and substance abuse. The psychological toll of these wars has been particularly harsh because of long exposure to combat-related stress over multiple rotations. Unlike the physical wounds of war that maim or disfigure, these conditions remain invisible to other service members, to family members and to society in general.

But emblematic of the great tragedy of war, especially this war, the toll these invisible wounds take on lives is great. Treatments to reverse or delay these injuries and disorders are critical and would benefit both the military and civilian populations alike, as approximately 1.7 million civilians sustain a traumatic brain injury as a result of car accidents, falls or other blows to the head every year.

The field of neuroscience, which is the study of the nervous system, has made significant advances in the last decade, providing new insights into the functioning of the brain and underlying disease mechanisms. Yet many questions remain, spanning the most fundamental, such as how to keep our brains healthy to the specific challenges of finding diagnostic tools for diseases like Alzheimer's or schizophrenia and determining ways to effectively treat TBI and PTSD.

The Federal Government has a vast array of research initiatives devoted to advances in neuroscience, and our ability to treat brain injuries and mental health disorders affecting both military and civilian populations. Many of these Federal initiatives involve extensive coordination with civilian and non-governmental sectors, including multi-disciplinary, multi-sector research programs and centers. We will hear about these efforts today.

Likewise, private foundations have played an increasingly important role in expediting the drug development process by bridging the gap between promising scientific discoveries and entrepreneurial expertise and funding needed to move them forward. The role of Government and private foundations has become especially critical to progress, because unfortunately, despite their immense profits, the pharmaceutical industry has been cutting back the research and development of central nervous system medications due to the high cost and high risk. As we will hear today, this could have a devastating impact on the drug development pipeline for neurologic disorders.

Without collaboration across all sectors—Government, industry and non-profit—neuroscience breakthroughs will stall and much-needed treatments for all Americans, especially for our men and women in uniform, who have endured injuries in service to their country, will not materialize. I hope this hearing will raise awareness about the critical role neuroscience has in developing treat-

ments to reverse or delay some of the impacts of neurologic or psychiatric disorders that millions of Americans are afflicted with, and will stimulate creative thinking about how to best advance discoveries and treatments for the broad spectrum of devastating brain-related injuries and disorders that continue to impose a heavy burden on individuals and society today.

Before I recognize our ranking member, Mr. Jordan, I want to say that the reason why this hearing came about is because Representative Kennedy, who has throughout a great period of time communicated to me his concern that we delve into this subject in a methodical way, that we contact all sectors, and we try to find ways of creating benefits for people through either recognizing the synergies that exist, or where there may be insufficient numbers, helping to make sure that resources at some point will be available to help facilitate greater coordination.

Representative Patrick Kennedy has been a tireless advocate for innovative, cross-disciplinary, collaborative biomedical research and has provided unwavering support to those with psychiatric disorders as well as returning veterans suffering from signature war injuries affecting the nervous system. So Pat, I want to thank you, not just on behalf of this committee, but on behalf of Members of Congress for your assistance in this vital area. You have made so many contributions to this Congress, but I think that as life goes on, this is going to be an area where you are leaving an enduring mark for your wisdom, your compassion and your sharing of your own experience with all of us. You are a person of great integrity and courage. I am honored to have served with you.

At this point, I would recognize the ranking member, Mr. Jordan.

[The prepared statement of Hon. Dennis J. Kucinich follows:]

Opening Statement
Dennis Kucinich, Chairman
Domestic Policy Subcommittee
Oversight and Government Reform Committee
"From Molecules to Minds: The Future of Neuroscience Research and Development."
September 29, 2010
2203 Rayburn HOB
2:00 P.M.

Good Afternoon. Today's hearing will address the critical need for better treatments for neurologic and psychiatric disorders and how the neuroscience community can best facilitate research to advance and accelerate discovery of treatments and cures.

Every year, the more than 1,000 disorders of the brain and nervous system result in more hospitalizations than any other disease group, even more than heart disease and cancer. Neurological illnesses affect more than 50 million Americans annually, at costs exceeding $460 billion. Neuropsychiatric illnesses, like schizophrenia, mood disorders, and autism, are the leading cause of disability in North America and Europe. In the United States, the cost in lost earnings due to psychiatric disease is estimated conservatively to be $200 billion per year. The toll of brain related disorders is enormous for individuals and families.

Veterans returning from wars in Iraq and Afghanistan have been particularly hit hard by neurologic disorders. Traumatic brain injury (TBI)--defined as a disruption in brain function that is caused by a head injury--has become known as one of the "signature wounds" of the wars in Iraq and Afghanistan, because of insurgents' heavy use of explosive devices, and armor which has better protected soldiers from life-threatening injuries. A disproportionately high number of returning military personnel also struggle with psychological health issues like post traumatic stress disorder (PTSD), clinical depression, anxiety disorder, sleep disturbances, or substance abuse. The psychological toll of these wars has been particularly harsh because of prolonged exposure to combat-related stress over multiple rotations. Unlike the physical wounds of war that maim or disfigure, these conditions remain invisible to other service members, to family members, and to society in general. But emblematic of the great tragedy of war, especially this war, the toll these invisible wounds take on lives is great. Treatments to reverse or delay these injuries and disorders are critical, and would benefit both military and civilian populations alike, as approximately 1.7 million civilians sustain a traumatic brain injury as a result of car accidents, falls or other blows to the head every year.

The field of Neuroscience, which is the study of the nervous system, has made significant advances in the last decade, providing new insights into the functioning of the brain and underlying disease mechanisms. Yet many questions remain, spanning from the most fundamental, such as, "How do we keep our brains healthy?" to the specific challenges of finding diagnostic tools for diseases like Alzheimer's or Schizophrenia and determining ways to effectively treat TBI and PTSD.

The federal government has a vast array of research initiatives devoted to advances in neuroscience and our ability to treat brain injuries and mental health disorders affecting both military and civilian populations. Many of these federal initiatives involve extensive coordination with civilian and non-governmental sectors, including multi-disciplinary and multi-sector research programs and centers. We will hear about these efforts today. Likewise, private foundations have played an increasingly important role in expediting the drug development process by bridging the gap between promising scientific discoveries and the entrepreneurial expertise and funding needed to move them forward. The role of government and private foundations has become especially critical to progress because unfortunately, despite their immense profits, the pharmaceutical industry has been cutting back their research and development of central nervous system medications due to the high cost and high risk. As we will hear today, this could have a devastating impact on the drug development pipeline for neurologic disorders.

Without collaboration across all sectors – government, industry, and nonprofit– neuroscience breakthroughs will stall and much-needed treatments for all Americans, and especially for our men and women in uniform who have endured injuries in service to their country, will not materialize. I hope this hearing will raise awareness about the critical role neuroscience has in developing treatments to reverse or delay some of the impacts of neurologic or psychiatric disorders that millions of Americans are afflicted with, and will stimulate creative thinking about how to best advance discoveries and treatments for the broad spectrum of devastating brain-related injuries and disorders that continue to impose such a heavy burden on individuals and society today.

My colleague Representative Patrick Kennedy has been a tireless advocate for innovative, cross-disciplinary, collaborative biomedical research, and has provided unwavering support to those with psychiatric disorders and returning veterans suffering from signature war injuries affecting the nervous system. I want to recognize him and thank him for his assistance with putting this hearing together and look forward to his participation today.

Mr. JORDAN. Thank you, Mr. Chairman. Let me too thank you for having this important hearing and for the work that Congressman Kennedy has done on this subject.

I have a meeting I have to get to in a few minutes, so in the interest of time I will ask the chairman if I can just submit my opening statement for the record.

Mr. KUCINICH. Without objection, so ordered.

Mr. JORDAN. Thank you.

Mr. KUCINICH. Thank you, Mr. Jordan, for your presence.

Mr. Kennedy, the Chair recognizes Mr. Kennedy.

Mr. KENNEDY. Thank you, Mr. Chairman. I really appreciate those very generous and kind remarks. And of course, Ranking Member Jordan, thank you for your being here to help kick this important hearing off.

And to my other colleagues, Mike Thompson, whose work in this area but also whose service today is highlighted because of his service to our country as a veteran in our military and that perspective that he brings and his work in this area. It is so appreciated. And Mr. Foster, thank you very much both for your being here and your efforts.

I want to thank you, Mr. Chairman, for putting this hearing together, and also your staff, who have been so instrumental. Jaron Bourke and Claire Coleman, who have been helpful, and Justin Baker, and all those who have been so critical in putting this event together. And my own staff, I want to thank Dan Murphy and Laurel Havis and my whole office for the work that they did in putting up with my aggravation at trying to get all this pulled together. They have just been the best and I want to thank them tremendously for this.

I have Chris Cann, who does all my veterans events in Rhode Island, I want to acknowledge he has put together a veterans diversion program for those ending up in our criminal justice system because of their wounds on this war, which are at ever-higher rates. We are doing that on October 25th in Rhode Island. I thank Chris for his work on that. And I want to thank John Sack for all the efforts that he put in as well.

Mr. Chairman, I also want to acknowledge some real other heroes here in this audience, not the least of which has been the former Secretary of Veterans Affairs, former U.S. Senator, but most important to all of us, an American hero in the true sense of the word, and that is Max Cleland.

[Applause.]

Mr. KENNEDY. We have an amazing lineup of people who have come to testify today. I want to thank all of them for being here, and say we are really at a point today when we are going to examine where we are today in neuroscience. And most importantly, what the stage is for us to set for us to really move forward much faster, more effectively and certainly to deliver the answers to neurological disorders and disability. Now more than ever, because of how it affects our American heroes, our Nation's veterans, the signature wounds of this war, brain injury and PTSD. We have the biggest burden of illness amongst the civilian population, but the civilian population today is going to be looking to the fact that our heroes are going to be the catalyst to bring us to one mind on brain

research. No more divisiveness; let's unify, let's get behind our veterans. When they win it, we all win it, as is always the case with our Nation's heroes, and in this case especially.

So we have a bunch of great testimony today. We will learn from those in the civilian sector how they can be helpful in their research to help our veterans, which should be our No. 1 priority.

So thank you, Mr. Chairman. I appreciate the opportunity to have an opening statement. I look forward to the questions.

Mr. KUCINICH. Thank you. The Chair recognizes Mr. Foster.

Mr. FOSTER. I yield back.

Mr. KUCINICH. The Chair recognizes Mr. Thompson.

Mr. THOMPSON. Thank you, Chairman Kucinich. Thank you for having the hearing and thanks to you and Representative Kennedy for inviting me to provide testimony today. My thanks to everyone who is here who recognizes this as not only a huge problem, but one that we can really get ahead of the curve on.

Mental illness impacts us all a great deal. The chairman pointed out the financial cost. While staggering, I think those dollar costs really pale in comparison to the heartbreak and the pain that families go through because of mental illness. With one in six of our adults in the country with diagnosable mental illness, it is really hard to find a family that isn't somehow touched by mental illness. As Patrick Kennedy said, our veterans are certainly a cause that we call can rally around. I am pleased to be able to say something on their behalf, and honored to be in the same hearing room with Senator Cleland, who is in fact a true hero.

We see more of our military personnel returning from Iraq and Afghanistan not with physical injuries, although they are a huge issue, important issue as well, but with mental injuries including PTSD, anxiety disorder or depression. So the call for research and support for a cure for brain illness grows louder and louder each time one of these veterans returns home. Reports indicate that 19 percent of Iraq war veterans and 11 percent of Afghanistan veterans suffer from mental illness.

The brain has been called the last frontier for medicine. And the time for that to end, I believe, is right now. It is time to bring together all of the different groups, including the Federal Government, the Congress, private industry, academia, everyone who has an interest in brain illness, to fully explore and to tackle this problem once and for all.

Every year in my congressional district, they hold the single largest fundraiser for mental health. It is called the Staglin Music Festival for Mental Health. And the proceeds from this fundraiser, the annual fundraiser, has now reached over $94 million. It is used to find research, to find better treatments and cures for schizophrenia, bipolar disorder and depression.

Another great hero who is with us today is Garen Staglin, in the front row. I don't know where his wonderful wife, Shari, is, if she is here or not. But the two of them work tirelessly for mental health and to raise the money to provide research funding for mental health. Their work to find a cure and to improve treatment for brain illness is inspired, and it is driven by a very personal story. In 1990, their son was diagnosed with schizophrenia. It was heartbreaking, it was a scary time for them and for their son.

But they took that heartbreak and they turned it into a benefit for everyone who cares about the advancement of mental health. In 1995, they started the International Mental Health Research Organization, which raises money for mental health research, collaborates and affiliates with organizations, and works to build awareness of scientific achievements in the field of mental health research.

The Staglins are very fond of saying the rewards are much greater if you run toward the problem, not away from it. We are fortunate that both Garen and Shari are running toward the problem of mental health and not away from it. The rewards, as I mentioned, have been great. So I want to make sure we recognize that they are making an immediate difference in the lives of millions of people. And I am really proud that you are here, Garen, and of the work that you are doing.

I too would like to join the chairman in recognizing our friend and colleague, Congressman Kennedy, for his work on mental health issues. He has been tireless, the entire 12 years that I have been in Congress, I don't know anyone who has worked any harder on any single subject than Patrick has worked on this. He has done so much good for so many people.

It really saddens me that you are leaving Congress, because so many people are going to lose, in Congress, a great advocate. I know you will always been working on this stuff, but he is just a tireless fighter. So I want to pledge to you, Patrick, that I will keep doing everything you tell me to do to make sure that we can get ahead of this. Everything you tell me to do in regard to working on mental illness.

Mr. KENNEDY. Good thing you made that distinction. [Laughter.]

Mr. THOMPSON. Everyone that has said it is right on, now is the time, and the emphasis on our veterans, I think it just punctuates the need to really double down and get this done. I thank you very much and I yield back and thank you for letting me testify.

Mr. KUCINICH. I thank the gentleman. Any other Members who appear will be given 5 legislative days to be able to make an opening statement.

Mr. KENNEDY. Mr. Chairman, Congressman Walter Jones has arrived.

Mr. KUCINICH. Congressman Jones, do you have a statement that you want to make?

Mr. JONES. Yes, Mr. Chairman.

Mr. KUCINICH. Without objection, come on up here, have a seat. This is Congressman Walter Jones from North Carolina, Republican Member. Have a seat.

Mr. JONES. Thank you, Mr. Chairman. Nothing like being late. Thank you.

I have Camp LeJeune Marine Base in my district. We have had a number of suicides of Marines who have been frequently deployed. We are having more problems with families staying together. I want to thank Patrick Kennedy for taking the lead on this and asking me to join you, Mr. Chairman, and the other Members here.

My biggest concern is that at some point in time in the very near future, we are not going to be able to do what we should do for

those who are suffering from PTSD and TBI. So I wanted to be here today to listen, to learn and to also be very proactive with my friends.

Thank you.

Mr. KUCINICH. I thank the gentleman. Members who appear once the testimony begins will be given five legislative days to submit statements for the record.

Before I begin introducing our panel of witnesses, I apologize for being a few minutes late, but I ran right into the room and focused on my script and getting the hearing off and running. Had I noticed Max Cleland in the room, I would have spoken as some of my colleagues have to his exemplary service to our country in so many ways.

When I came into Congress, Max was one of the first people I consulted with on that other side of the Capitol. And I have to say, Max, you honor us by your presence in this room. I am so grateful that you continue to serve in other capacities. You know how I feel about you and when I saw you, I thought, wow, Cleland is in the audience. So thank you.

Our first panel: Dr. Thomas R. Insel, M.D., is the Director of the National Institute of Mental Health. His tenure at NIMH has been distinguished by groundbreaking findings in the areas of practical clinical trials, autism research and the role of genetics in mental illnesses. Prior to his appointment as NIMH Director in fall 2002, Dr. Insel was professor of psychiatry at Emory University.

Next, Dr. Walter J. Koroshetz, who is Deputy Director of the National Institute for Neurological Disorders and Stroke. Before joining NINDS, Dr. Koroshetz served as vice chair of the neurology service and director of stroke and neurointensive care services at Massachusetts General Hospital. He is also professor of neurology at Harvard Medical.

Joel Kupersmith, M.D., Dr. Kupersmith is Chief Research and Development Officer for the Veterans Health Administration, U.S. Department of Veterans Affairs. Prior to joining VA, Dr. Kupersmith was dean of the School of Medicine and Graduate School of Biomedical Sciences and vice president for clinical affairs at Tech University.

Finally, Terry Rauch, Ph.D., currently serves as the Director of the Defense Medical Research and Development Program within the Office of the Assistant Secretary of Defense for Health Affairs. He has responsibility for the defense health program R&D portfolio. He has over 30 years of experience in many facets of the military health system and has held numerous senior level positions in the Army and the Office of the Secretary of Defense.

I want to thank each and every one of the distinguished panelists for their presence here today. It is a policy of the Committee on Oversight and Government Reform to swear in our witnesses before they testify. I would now ask that each of the witnesses rise, raise your right hands.

[Witnesses sworn.]

Mr. KUCINICH. Thank you very much.

Let the record reflect that each of the witnesses answered in the affirmative. I would now ask that each witness give a brief summary of your testimony, keep the summary under 5 minutes in du-

ration if you can. Your complete written statement will be in the hearing record.

I don't know if you can see the clock there, there is a, you have an even better view, but we have a little box there with colored lights. Let's begin with Dr. Insel. And thank you for being here, sir. Please start.

STATEMENTS OF THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH; WALTER J. KOROSHETZ, M.D., DEPUTY DIRECTOR, NATIONAL INSTITUTE FOR NEUROLOGICAL DISORDERS AND STROKE; JOEL KUPERSMITH, M.D., CHIEF RESEARCH AND DEVELOPMENT OFFICER, VETERANS HEALTH ADMINISTRATION, U.S. DEPARTMENT OF VETERANS AFFAIRS; AND TERRY RAUCH, PH.D., DIRECTOR, DEFENSE MEDICAL RESEARCH AND DEVELOPMENT PROGRAM, OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS, DEPARTMENT OF DEFENSE

STATEMENT OF THOMAS R. INSEL, M.D.

Dr. INSEL. Thank you, Mr. Chairman. I really appreciate the committee's interest in this issue, and I also want to thank Congressman Kennedy for what has been a very long period of passionate leadership. We are going to miss you tremendously as you move to your next post. I can only hope that you will come work for us at some point.

Mr. KENNEDY. I thought I already was. [Laughter.]

What do you think all those appropriations were over there?

Mr. KUCINICH. Regular order. Go ahead.

Dr. INSEL. The National Institute of Mental Health is part of the National Institute of Health, part of the Department of Health and Human Services. And Dr. Koroshetz and I will talk about this perspective on these disorders and the urgent needs we have from the NIH side both for NINDS and NIMH. I think rather than go into the details of my testimony, which you have in front of you, I would like to just take you through pictures that may be more helpful for you to expand on some of the things, Chairman Kucinich, you already mentioned in your opening statements.

So if I can have the next slide, let me talk a little bit about what it is when we talk about this burden of illness that people refer to. When we think about this in numerical terms, we use something called the disability adjusted life years, an unfortunate term, that has to do with how many years are lost to disability. You can see from this graph, I hope, from the World Health Organization, numbers put together in 2008, that neuropsychiatric illnesses broadly represent almost 30 percent of all the disability form all medical causes for non-communicable diseases. So that ranks them well above heart disease, cancer and many of the things that many of us often think about as the big killers.

Part of the reason why the disability rate is so high is that some of these actually become chronic diseases, and they begin early, and as was already mentioned, common. So the high prevalence also drives these kinds of numbers.

In the next slide, you'll see that if you break this down, the next slide, please, I am sorry, we skipped one. Can we go back one? That the actual disorders within this category include depression, alcohol, Alzheimer's disease and many others, with depression being really the No. 1 driver for the sources of disability.

It is really a powerful statement that so much of medical disability is driven by this one group of illnesses, all of which occur quite early in life. We tend to think of these as the chronic disorders of young people. But it is not just that they are chronic. They are also, not only that they cause morbidity, they also are a source or mortality.

You will see in the next slide that suicide, which 90 percent of the time involves a mental illness, accounts for over 34,000 deaths each year in this country, which is an extraordinary number when you put this in context. As you will see in the next bullet, that is almost double the number of homicides. And at this point, based on the numbers released about a week ago from the National Safety Transportation Board, more than the number of deaths from traffic fatalities, which is just extraordinary.

Now, we have a whole criminal justice system to deal with the homicides and a whole transportation safety system to deal with traffic fatalities. One might ask, what do we have by comparison to handle this growing issue of suicides in America. It is not only suicides that are driving mortality, but lots of other sources of medical illness.

You can see in the next bullet that in fact, in the United States, the life expectancy today for someone with a serious mental illness is about 56 years, which according to what I looked at on Google about a week ago is about the life expectancy today in Bangladesh. So this is not where we want to be in 2010.

It was already mentioned before about the economic costs involved here. In the next slide, you will have a picture of that. Maybe this will be difficult for you to see, but the last column over shows that, if you will hit the next bullet, that it is about $57½ billion in health care costs that go to mental illnesses, which is just about what we are spending each year for cancer in the United States. What is dramatic about that are two things: first, that is a huge increase from where we were a decade ago, so these are really now driving upwards relative to many other medical sources. And maybe second, even more importantly, this barely captures the real costs, economically. Because most of the costs of mental illnesses are outside of the health care system.

Next bullet, you will see, the costs of lost earnings, of welfare, next, incarceration, homelessness, school and home care, all the places where most care or failure of care from mental illnesses really play out. Next, so we estimate that the actual total comes to about $1,000 per American per year that we are spending, the way we do this now, to provide what is obviously mediocre help to people with these very disabling and chronic illnesses.

Next, if that is the bad news, I need to tell you that we are not just facing huge challenges, but really unprecedented opportunities. And I wanted to take just a couple of minutes, if I can, to flesh those out. There are two that I will speak of very quickly. The first has to do with the recognition in the next bullet that these are in-

deed brain disorders, they are not brain disorders in the way stroke or Alzheimer's might be, but they are disorders of brain circuits. We have been able now to define those with the help of genetics and with the help of new technologies.

We also now recognize, in the next bullet, that these are developmental disorders. I mentioned that they start early in childhood most of the time, at a time when the brain is still developing. But this gives us a real opportunity for thinking about how to intervene. We will see in the next slide that we have a whole range of technologies that have been developed over the last 5 to 10 years that are real game-changers here. For the first time, we can study brain circuits with the kind of precision that we can only dream about 15 to 20 years ago. And that has made this a tractable problem, where we should expect to see tremendous progress over the next decade.

You will see in the next slide, and we will just run through these very quickly, that we have already begun to describe the circuit basis of most of the major disorders. This is depression. Next is obsessive compulsive disorder. Next, PTSD, one that we are going to talk much more about this afternoon.

But in each case, we have begun to identify the major nodes in the brain, the importance of the pre-frontal cortex, which is really the kind of great last frontier for neuroscience. It has begun to open up real opportunities for new therapeutics.

Let me finish up by saying that this is an enormous challenge. I don't want to give you for a moment the sense that we have mastered this problem. I would like to say that we know about 2 percent of what we need to know. But we need to do this in a way that as Congressman Kennedy said will be collaborative and will be a joint effort.

There is an old African proverb that says if you need to go fast, go alone, if you need to go far, go together. And we will need to do both.

So I will show you in the next couple of slides how we are thinking about that. In the next slide, you will see, let's go ahead and run through this. We have a number of projects with the VA, with a total of about nearly 100 grants across 23 States with about $41 million in investments that we are now doing. And just keep hitting the bullets, because we don't have time to go through much of this. But I want to make sure you understand that this is by no means a siloed effort. We are not balkanized any longer. There is a lot of effort going on, both intellectually and practically, to make sure that we are working very closely together.

And finally, in the last slide, let me just say that probably the largest effort that we have mounted at the NIMH in the past 18 months has been the Army Stars initiative, which we are doing very closely with the Department of Defense. This really responds to the increase in suicide, which you have heard a little bit about already, the increase has gone to 160 in 2009, and 239 if you include reserve forces as well. In a recent publication, Vice Chief of Staff Pete Corelli mentioned that from his perspective, it appears that we may be losing more soldiers to suicide and to high risk behaviors than we are to combat. This has to be the highest priority.

We have now entered in with them a very large study. We call it a Framingham-like study, because it is really looking at the entire Army and trying to understand risk and resilience for the forces, and providing information back as quickly as we can to promote resilience and to reduce risk.

So if we can just put up the last slide. I want to thank you for your leadership in this area, Mr. Chairman, and I look forward to having a chance to discuss any of this much further with you.

[The prepared statement of Dr. Insel follows:]

Testimony
Before the Subcommittee on Domestic Policy
Committee on Oversight and Government Reform
United States House of Representatives

Statement for hearing entitled,
"From Molecules to Minds: The Future of Neuroscience Research and Development"

Statement of
Thomas R. Insel, M.D.
Director
National Institute of Mental Health
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 2:00 p.m.
September 29, 2010

Good morning Chairman Kucinich, Ranking Member Jordan, and members of the Subcommittee. I am Thomas R. Insel, M.D., Director of the National Institute of Mental Health (NIMH) at the National Institutes of Health, an agency in the Department of Health and Human Services (HHS). Thank you for this opportunity to present an overview of the current state of neuroscience research at NIMH, with a particular focus on our efforts to address mental disorders affecting U.S. veterans and military personnel, and our efforts to partner with both private industry and other Federal agencies to discover, develop, and pursue new treatments and diagnostic tools for brain disorders affecting all Americans. In my testimony, I will briefly review clinical challenges, treatment options, research opportunities, and some new efforts from NIMH.

NIMH's mission is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. The burden of mental illness is enormous. In a given year, an estimated 13 million American adults (approximately 1 in 17) suffer from a seriously disabling mental illness.[1,2] According to the World Health Organization, mental disorders are the leading cause of medical disability in the United States and Canada.[3] Suicide is the 10th leading cause of death in the United States, accounting for the loss of approximately 34,500 American lives each year, nearly twice the number from homicides.[4,5] More than half of local jail and state prison inmates suffer from mental disorders, though fewer than half in each population have ever received treatment.[6] In contrast to many other chronic medical conditions, mental disorders typically begin at an early age, usually before the age of 30. Mental disorders, such as schizophrenia, depression, and

[1] Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, 2005 Jun;62(6):617-27.
[2] U.S. Census Bureau Population Estimates by Demographic Characteristics. Table 2: Annual Estimates of the Population by Selected Age Groups and Sex for the United States: April 1, 2000 to July 1, 2004 (NC-EST2004-02) Source: Population Division, U.S. Census Bureau Release Date: June 9, 2005.
[3] The World Health Organization. The global burden of disease: 2004 update, Table A2: Burden of disease in DALYs by cause, sex and income group in WHO regions, estimates for 2004. Geneva, Switzerland: WHO, 2008.
[4] Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS). (www.cdc.gov /ncipc/wisqars)
[5] United States Department of Justice, Federal Bureau of Investigation. (September 2009). *Crime in the United States, 2008.* (www.fbi.gov/ucr/cius2008/index.html)
[6] James DJ, Glaze LE. *Bureau of Justice Statistics special report: Mental health problems of prison and jail inmates.* Washington, DC: Office of Justice Programs, U.S. Department of Justice; 2006.

bipolar disorder, are increasingly recognized as the chronic medical illnesses of young people. Overall, 13.1 percent of children ages 8-15 are clinically diagnosable for a mental disorder, though only slightly more than half have received treatment for their disorder.[7] Mental disorders can be seriously disabling, life-threatening illnesses for which we need reliable diagnostic tests, new treatments, and effective strategies for prevention. Today's treatments are not good enough.

The annual economic costs of mental illness in the United States are staggering. According to the most current estimates, the direct costs of mental health treatment represent 6.2 percent of all health care spending,[8] which, according to the Centers for Medicare and Medicaid Services (CMS), totals 15.8 percent of the gross domestic product. Indirect costs associated with mental illness, which include all non-treatment-related costs such as lost earnings, Social Security disability payments and homelessness account for even greater expenditures than those associated with direct mental health care. Serious mental illnesses cost the United States at least $193 billion annually in lost earnings alone.[9] A conservative estimate places the total direct and indirect annual costs of mental illness at well over $300 billion.[10]

While we have long known that mental disorders are brain disorders, recent research has begun to re-frame these illnesses as disorders of brain development. Between infancy and adulthood dramatic changes are taking place in the brain, not only in size, but also in the structure and function of brain circuits. The behavioral and cognitive symptoms of mental disorders may actually represent late stages of processes gone awry earlier in development. By comparing trajectories of healthy development to those of mental disorders, we can better understand when development moves off course. Redefining these illnesses in terms of developmental trajectories provides unprecedented promise for the prediction and prevention of mental disorders, as well as opportunities to harness this knowledge to improve diagnosis and treatments.

---

[7] Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. *Pediatrics*, 2010 Jan; 125(1): 75-81.

[8] Mark TL, Levit KR, Coffey RM, McKusick DR, Harwood HJ, King EC, Bouchery E, Genuardi JS, Vandivort-Warren R, Buck JA, Ryan K. *National Expenditures for Mental Health Services and Substance Abuse Treatment, 1993-2003*. SAMHSA Publication No. SMA 07-4227 Rockville, MD: Substance Abuse and Mental Health Services Administration, 2007.

[9] Kessler, RC, Heeringa S, Lakoma MD, Petukhova M, Rupp AE, Schoenbaum M, Wang PS, Zaslavsky AM. The individual-level and societal-level effects of mental disorders on earnings in the United States: Results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2008 Jun;165(6):703-11.

[10] Insel TR. Assessing the economic cost of serious mental illness. *Am J Psychiatry*. 2008 Jun;165(6):663-5.

Research = Hope: Fostering Innovations in Diagnosis

One of the greatest challenges in managing mental disorders in the post-genomic era is to "catch up" with the rest of clinical medicine with respect to diagnostic, prognostic, therapeutic, and preventive strategies. Healthcare providers in many specialties are now able to call upon a vast array of clinically relevant biomarkers to accomplish this cardinal task. By contrast, healthcare providers treating mental disorders rely almost exclusively on clinical observation and historical data obtained from patients and other informants. Despite tremendous progress in basic neuroscience, not a single biomarker has been developed with established clinical use in the management of major mental disorders outside the area of substance abuse. To break this logjam, NIMH has funded the study Establishing Moderators/Mediators for a Biosignature of Antidepressant Response in Clinical Care (EMBARC) to identify integrated panels of potential biomarkers (i.e., biosignatures) that are predictive of treatment outcomes in major depressive disorder (MDD). NIMH expects to commit approximately $12 million to this initiative. In addition, biomarker efforts have been launched for autism spectrum disorder, schizophrenia, and post-traumatic stress disorder (PTSD).

The concept is straightforward. If mental disorders are brain disorders, then biological or subtle cognitive changes might be detected long before the full syndrome becomes manifest with psychosis or a severe mood disturbance. One of the first rules of medicine is the earlier we intervene, the better the outcome. Biomarkers or biosignatures would permit earlier intervention with greater promise of prevention or full recovery, an approach we have called "preemptive medicine."

Research = Hope: New Treatments

For more than five decades, NIMH has supported high-quality clinical research on the efficacy of psychosocial, somatic, and pharmacological treatments for mental disorders. Randomized clinical trials have helped us identify effective therapeutic interventions for nearly all mental disorders. While we have treatments for all disorders, we do not have treatments for all patients. For too many, current treatments are not sufficient. And for most, current treatments fall far short of a cure. Research with new treatments offers new hope to those with serious mental illness.

PTSD: Researchers today view PTSD as a brain disorder, related to specific circuits in the brain necessary for overcoming or extinguishing fear.[11] Recently, scientists have discovered that "fear extinction" in the brain is an active learning process, not a passive process of forgetting.[12] Researchers have identified at least one specific chemical that may help to improve the brain's process of extinction learning, and it is currently being tested as an adjunct for treating PTSD.[13] And they have identified periods at which people are most receptive to treatment that may facilitate fear extinction. New research suggests that therapy administered within a certain time frame after the traumatic event may enhance recovery.[14] This research and other studies provide hope that our new understanding of fear extinction can be applied to the development of new behavioral therapies to promote more rapid recovery among those suffering from PTSD.

Schizophrenia: Much of the disability of schizophrenia results from the cognitive deficits, such as memory and attention problems, associated with this complex brain disorder. Current antipsychotic medications do not resolve these cognitive problems. A major effort underway involves development of novel medications and cognitive interventions targeted at this aspect of schizophrenia. In addition to these efforts to develop new interventions to hasten recovery, NIMH recently launched the Recovery After an Initial Schizophrenia Episode (RAISE) project—a clinical trial that will develop and test the coordinated intervention of existing approaches in the early stages of the illness when symptoms may be most responsive to treatment. Importantly, the interventions being tested will be designed from the outset to be readily adopted in real-world health care settings and quickly put into practice.

Mood Disorders: MDD and bipolar disorder (BD) are both characterized by depressive episodes which are long-lasting and difficult to treat. Antidepressants typically take weeks to have an effect, and many patients do not respond adequately to existing medications. Recent studies in patients with either form of mood disorder demonstrate that ketamine can resolve depressed mood within four hours instead of the four weeks required for existing

[11] Milad MR, Quirk GJ Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*. 2002; 420:70 –74.
[12] Bouton ME. Context and behavioral processes in extinction. *Learn Mem*. 2004; 11:485– 494.
[13] Walker DL, Ressler KJ, Lu K-T, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *J Neurosci*. 2002; 22:2343–2351.
[14] Schiller D, Monfils MH, Raio CM, Johnson DC, LeDoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature. 2010 Jan 7,463(7277): 36-37.

antidepressants.[15] The response to ketamine lasts an average of about a week. This work adds to evidence that compounds in the class to which ketamine belongs have potential as rapid and effective medications for depression, including bipolar depression. The potential for side-effects makes ketamine an impractical drug for standard use, but it provides a way to test this approach for developing novel treatments that act more rapidly than existing ones. In short, we are witnessing the beginning of a paradigm shift in how we treat depression and bipolar disorder—from slow and chronic treatment to rapid and acute care.

Advancing Mental Health Research through Collaboration and Partnership

NIMH's mission is not merely to reduce the symptoms and disability associated with mental disorders, but to promote recovery, to extend healthy life, and ultimately, to discover preventive interventions. The success of the Institute's mission depends on the effective collaboration of all stakeholders in the field of mental health. For example, NIMH, the Department of Veterans Affairs (VA), and the Department of Defense (DoD) are committed to research collaborations that will improve the mental health and well-being of military personnel and veterans. Not only is this important to the VA and military, but the knowledge we gain from research collaborations will be critical to the civilian sector: many veterans seek care within their home communities and the problems of soldiers are shared by the society they serve. Moreover, although research conducted on the mental health of military personnel is most immediately applicable in a military context, we expect that the knowledge gained will benefit civilians as well. Although rates of suicide have traditionally been lower for members of the U.S. Army than rates for civilians in the same age range, the rate in the Army began to increase in 2004, doubled by 2008, and reached 160 deaths in 2009 (239 including its Reserve component), exceeding the comparable civilian rate and ranking as the third largest cause of death. For the month of June 2010, the Army reported an astonishing 32 suspected suicides—a record high. Commenting on the high rates of 2009, a recent Army report entitled, Health Promotion, Risk Reduction, Suicide Prevention[16] noted, "If we include accidental death which is frequently the result of high risk

[15] Diazgranados, N, et al., A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 2010, 67(8):793-802.
[16] Please see http://www.army.mil/-news/2010/07/28/42934-army-health-promotion-risk-reduction-and-suicide-prevention-report/index.html?ref=home-headline-link0

behavior (drinking and driving, drug overdose, etc.), we find that less young men and women die in combat than die by their own hands. Simply stated, we are often more dangerous to ourselves than the enemy."(p. 11).

In an effort to reduce this increasing rate of suicide among Army personnel, NIMH and the Army have partnered to conduct the Study to Assess Risk and Resilience of Service Members (Army STARRS)—the largest mental health study of military personnel ever undertaken. The study's goal is to identify, as rapidly as possible, risk and protective factors that will help the Army develop effective strategies for reducing rising suicide rates and addressing associated mental health problems among service members. Army STARRS was officially launched in late 2008 when NIMH and the Army partnered to address the increasing rate of suicide. Over the early months of this effort, both parties realized the need to focus on resilience as well as risk. NIMH and the Army modeled the Army STARRS approach after the Framingham study[17] of cardiac death to conduct a broad investigation of factors leading to adverse outcomes, including suicide, depression, PTSD, and high risk self-destructive behaviors. Accordingly, Army STARRS will have many components, from retrospective studies of completed suicides to prospective studies that will identify the most important predictors of risk and resilience.

In addition to our partnerships with DoD and the VA, we have sought out opportunities to engage other Federal agencies to promote mental health. One such partnership, with HHS's Substance Abuse and Mental Health Services Administration (SAMHSA), is designed to evaluate suicide hotline training. Crisis hotlines are one of the oldest resources for suicide prevention in the United States. Yet widespread concerns exist about the clinical effectiveness of these services and the extent to which high-risk individuals are using these resources. NIMH is supporting a project to evaluate the effectiveness of a new training program for telephone crisis counselors at suicide hotline centers. The National Suicide Prevention Lifeline (NSPL), the nation's leading source of immediate help for those dealing with suicide-related issues, funded by SAMHSA, is carrying out the training program across its network of crisis centers. This project is the first controlled study of how trained crisis counselors assess and refer callers,

[17] The Framingham Heart Study is a long-term, ongoing cardiovascular study on residents of the town of Framingham, MA. The study began in 1948 with 5,209 adult subjects from Framingham.

and will provide the first rigorous analysis of the effectiveness of the Applied Suicide Intervention Skills Training (ASIST) gatekeeper program. ASIST involves silent monitoring of calls and follow-up telephone interviews with callers to the hotline, which are used to provide information on the effectiveness of training and the impact of hotline services. In addition, this research will examine the relationships among training for crisis counselors, crisis counselors' performance, and crisis call outcomes. The study findings will provide critically needed data to inform policy decisions and plans regarding the optimization of a network of services for imminently suicidal individuals across the United States.

Conclusion

For the millions of Americans living with mental disorders today, we do not yet have all the answers. Nonetheless, research provides great hope for the future. With the leadership of our colleagues in the military and the VA, there is increasing public recognition that mental disorders are brain disorders: real disorders with real treatments. Genetics and neuroscience are revolutionizing the diagnosis and treatment of mental illness. There has never been a greater need for progress and never a greater opportunity. NIMH is determined to accelerate progress towards prevention, recovery, and cure.

Thank you for this opportunity to present an overview of some of the exciting recent discoveries about the science of mental illness. I look forward to answering your questions.

Mr. KUCINICH. Thank you very much.
Dr. Koroshetz, please.

STATEMENT OF WALTER J. KOROSHETZ, M.D.

Dr. KOROSHETZ. Thank you very much, Chairman. I am going to talk a little bit maybe deeper in the weeds than Tom went. But I think a lot of the things are very complementary. I am going to talk about what we are doing to try to understand how the brain works and how we are working together, actually stressing the collaborative piece on developing treatments for brain disorders.

Next slide. So our problem is that we have a lot of disorders. There are, some people count 600 neurological disorders that our institute is trying to attack. But the message here is that we have to go one by one to get a drug. But to make real progress, we need basic science discoveries that are going to cut across multiple, as opposed, because one-by-one is going to take such a long time.

Next slide. So this slide basically gets away from the numbers and just reminds you of the real tragedy that occurs when you lose part of your nervous system function. It really defines what is a human being and what makes us different from the next person. And so there is real personal tragedy behind all of these diseases, unfortunately.

For people who are interested, I refer you to the Web site. We actually did a very kind of in-depth, bare bones, look at how the NINDS works, where we need to improve. We got experts from the extramural community, different Government agencies, industry, academia, disease organization leaders, to look at it. We brought them in, we bared ourselves, showed them how the Institute works. We got very good recommendations to move forward.

And out of this, you can see the details on the Web site, but the mission is reaffirmed, which is to reduce the burden of neurological disorders through research. We think there are two main pillars on which this is going to stand. Firstly, we need to understand how the normal brain and nervous system develop. Much of what we think happens in repair when there is a brain injury is just beginning that developmental program all over again. So the more we learn about how the brain develops, we think the more we are going to know about how to effect repair once it is injured.

We need to know what goes wrong in diseases, and then we need to be able to translate this knowledge from basic and clinical discoveries into better ways to prevent and treat neurologic disorders. There are a number of other points here which you could read more about, but I am going to hit some of them as we go along.

Next slide, please. This point has come up already in the chairman's statements and hopefully will come up again. It is the fact that when push comes to shove, if you have a neurological disease, you need a particular treatment, a particular drug, a particular type of treatment that is going to help you. And it has to be specific. We eventually have to go from our basic knowledge to a very specific treatment.

If we don't do that, if we don't take advantage of our preeminence in biological sciences to translate to really what are commercial products at the end, the patients see no benefit, needless to say the economy sees no benefit from the Government's invest-

ment. And it has been said, major pharma is now shunning neurological disorders as unacceptable, risky investments. They have very high development costs. They have a high failure rate when they go into the clinic. And the more and more we know about the diseases, we get smaller and smaller markets for them to make profits on. So we have to try and solve this problem.

And the word that is used around NIH now is the word de-risk. So what NIH sees is that their role currently is to try to take basic knowledge, try and actually develop molecules that will be treatments and bring them as far along the pipeline as we can until the risk is so low that industry will pick them up. That is kind of the general idea.

The big problem, well, there are a lot of problems, but one of the big problems that we have hit is that if the sad but true statement that if you are a mouse and have disease X, don't worry about it, we can fix you. But if you are a human with disease X, you had better worry, because we don't have something.

So we have been able to do really well for the mice. The problem is, when we go from the mouse to the human, we are missing something. We need a bridge. And we talk about biomarkers, and maybe this will come up later. A biomarker in my mind is a way to bridge what we know from the animal disease to the human disease, so that we know when we go into the human, we hit this biomarker, it is going to give a high chance of success. If we just go into the human and treat the brain as a black box, then there is a lot of guesswork, a lot of things can go wrong.

That is the idea of this bridging biomarker. So there is a big emphasis now. You will hear about it particularly with regard to Alzheimer's disease, and this big ADNI project that is a public-private partnership to develop biomarkers for Alzheimer's disease drug development.

Next slide. NINDS does not work alone. We have so many disorders, we need everybody working together. We basically work very closely with tremendous numbers of really innovative neuroscientists that, most belong to the Society for Neuroscience, the professionals in neurology, surgical, psychiatry, emergency medicine. Many different professional societies. And these private organizations, these organizations that are disease related that have real motivation and dedication and persistence to galvanize communities are essential for us to carry out our mission and perform tremendous, really tremendous research now.

Next slide. Now, this is a really busy slide. And this is basically a slide of how we conceive of the pipeline going from, on the left, the basic science R01 investigative grants, which are the mainstream of the NIH investment, to really make the most of the innovation in the American scientist pool, to bring out new basic knowledge. And that is really the critical thing that everything is based upon.

But once you have that knowledge, someone who is interested in this other area has to go in and try to pick out from that knowledge something that is going to be a useful treatment. Then there are a number of steps one has to go through until you get to the proof of principle, and the animal model, show it working, and go into the human. So this is not rocket science, but it is a process.

It is well known to the pharmaceutical companies and now NIH is really getting interested in how we can move this further to the left, taking the risk out of drug development.

What I have listed here is a number of the programs that NINDS has in this arena. The ones in green are ones that we do with many institutes at NIH. The ones in blue are ones that we generally have disease organizations as our partners. And the ones in red are the ones we usually have industry as our partners.

And just a couple of points, just yesterday we announced that we will be working on a public-private partnership much like Alzheimer's disease, develop biomarkers for Parkinson's disease drug development. We have a network that we are going to set up that will be nimble, be able to move from disease to disease, to test the best therapies available coming out of neuroscience and biomarker informed trials. The NIH blueprint, important to know about the blueprint, it is all the institutes at NIH, they come together and they decide what they can do together as a group. Here they put together this neurotherapeutic grant challenge, which is trying to really fill the pipeline with really creative agents that can help many different neuroscience diseases, not just NINDS diseases or NIMH diseases, any neuroscience disease.

Next slide. In terms of brain injury research, we have been working really hard with our DOD and VA collaborators to try and make a dent in trying to do something that will improve the recovery of our soldiers and protect them potentially in the future.

So NINDS is a leading funding agency and has been for traumatic brain injury research. TBI is the leading killer of young adults. One of the couple of things we have done recently is we have set up, and I am the co-director of this, with Dr. Armstrong at the Uniformed Services University across the street, a center for TBI research. This is investigators at Walter Reed, National Navy Medical Center, Uniformed Services University and NIH. It is about 56 investigators working with a fairly good budget, trying to make a dent in many different areas of traumatic brain injury research. It is an intramural program at NIH and USU.

We have a common data elements project that has been done with a Federal interagency group that has members from almost any Federal agency that works in the area of TBI. What they have been working on most recently is standard ways of collecting data, so that no matter who is doing the study, what agency is funding it, they are collecting the same type of data, so this data can be combined and mined, and the value of the data goes up substantially.

We also are working on projects with DARPA. They have an amazing prosthetic arm. I don't know if anybody has seen it, but if you haven't, it is really worth it. Tremendous new prosthetic arm for upper extremity amputees. And we are funding projects so that soldiers will be able to control this from brain activity.

The NIH also participates in DOD grant review. We are working now with Uniformed Services and some of the other DOD groups to develop an MRI scanner that will just do brains, but can be small enough to be taken far afield into the military.

Finally, we do again have another phase three trial on progesterone ongoing in acute TBI. We are working with a military site to bring them into San Antonio TBI Level I trauma center.

Next slide. I am going to end really where the beginning is, and that is kind of in the basic science. I just want to tell this one story. There are lots of stories like this and the details change. But this is an example of how really basic science that you had no idea was going to be helpful to brain diseases, turns out that it really is.

So basically, these little pictures here are microbes. They are not even real bacteria, that is how primitive they are. But they have these channels in their membranes that when light is shined upon the membrane, the channels open. And really innovative scientists have been able to take this gene from these microbes, put it into viruses, transfect brain cells. Now the brain cells have these channels.

And they can go in with laser lights and with amazing temporal and spatial accuracy, they can then shine the light, the channels will open. Some of them will shut the cells off, depending on what channels, some will turn the cells on. And for the first time, with this technology, you can actually activate circuits in the brain, as opposed to what we did before, which was sent electricity in with a wire and nobody knew where the electrons went. This is really specific, really tremendous.

It has only been out a couple of years, you can see from these papers, that there is real disease-related work that has come from this stuff that started with microbes. So for instance, they have been able to show that when someone has a spinal cord injury, they lose their ability to breathe. They can now put these channels into mice with a spinal cord injury, activate the breathing circuits and the mice start breathing again.

So just a great example, lots of stories like this where the basic science, you can't tell where the advances are coming from. But a tool that comes out of this that you didn't have before and really allows a lot of breakthroughs.

Next slide. And that is basically what I wanted to say, it is short but I hope it was interesting and I would be happy to answer any questions. Thanks.

[The prepared statement of Dr. Koroshetz follows:]

Testimony
Before the Subcommittee on Domestic Policy
Committee on Oversight and Government Reform
United States House of Representatives

Statement for hearing entitled,
"From Molecules to Minds: The Future of Neuroscience Research and Development"

Statement of
Walter J. Koroshetz, M.D.
Deputy Director
National Institute of Neurological Disorders and Stroke
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 2:00 p.m.
September 29, 2010

Mr. Chairman and Members of the Committee,

Thank you for the opportunity to testify about neuroscience research—what we know, where we are going, and how we are translating advances in basic neuroscience to better health. I will give particular attention to collaboration and cooperation with the Department of Defense, the Veterans Administration, and other public and private groups and to traumatic brain injury (TBI), which is a major public health challenge for neuroscience that affects civilians of all ages, as well as active military and veterans.

STATUS and CHALLENGES of NEUROSCIENCE RESEARCH

How do the brain and the rest of the nervous system work— how do we move, perceive, think, feel, and, consciously and unconsciously, regulate the organ systems of our bodies? How do genes and the environment together shape the developing brain? What goes wrong in the hundreds of diseases that affect the nervous system? And, most importantly, how do we use what we have learned from neuroscience to improve health throughout life? These are the grand challenges for neuroscience.

Neuroscience has made remarkable progress in understanding the fundamental basis of how the brain develops and how it works. Scientists have identified molecules that control how specialized brain cells develop, find their places, and connect with one another in precise patterns. Research has revealed what drives the electrical activity of brain cells, how synapses work, and how these connections between nerve cells adjust their strength with experience. Understanding at the fine grain of molecules and cells has come a long way, and on the larger scale we know which areas of the brain are essential for most functions, but how cells and synapses come together as a working system to represent a memory, experience a perception, or plan a movement has been more elusive. Yet, even these "systems" questions are giving way to new technologies and insightful investigators. A technique called "brainbow"[1] can label each

[1] Livet et al. Transgenic strategies for combinatorial expression of fluorescent proteins in the nervous system. Nature 450:56-62, 2007

individual nerve cell and its long nerve fibers with one of a hundred different colors so that researches can trace connections of that cell in the tangle of thousands of others and even watch changes over time. Increasingly automated computer methods allow scientists to construct 3-D maps of the circuits formed by nerve cells. Similarly, on the functional side, "optogenetics"[2] precisely activates or inactivates nerve cells on command with focused light pulses, enabling scientists to parse out how circuits of interconnected nerve cells carry out complex analyses. Tying all of this together, better brain imaging technologies reveal in increasing detail which parts of the brain come into play as people carry out complex tasks, and brain imaging can highlight structural changes that occur in the brain during normal development, disease, response to drugs, and recovery from stroke or trauma. Now that we have much of the parts list for the brain, neuroscience is taking on the challenge of "putting the brain back together."

On the disease front, neuroscience has made substantial progress in understanding what goes wrong in the brain during disease, but we still have a long way to go. For genetic diseases, the progress has been most impressive. Teams of clinicians and geneticists have identified hundreds of gene defects that cause inherited disorders. This has led to animal models that mimic the human diseases, to insight about what goes wrong, and to rational strategies to develop therapies. Over the last several years, drugs targeted to key steps in the disease process have shown encouraging results in animal models for several inherited neurological disorders. For example, perhaps surprisingly, drugs have even reversed the developmental deficits[3] in animals that mimic neurofibromatosis, tuberous sclerosis, Down syndrome, and fragile X syndrome. Other intervention strategies, including gene therapy and stem cells, have shown similar promise in animal models of other inherited nervous system disorders, including Batten's disease[4] and Rett syndrome[5]. There is a sense of cautious optimism as these rationally designed interventions are moving from animal studies into clinical testing.

---

[2] Zhang et al. Optogenetic interrogation of neural circuits: technology for probing mammalian brain structures. Nature Protocols 5:439-56 2010

[3] Silva, A.J. and D. Ehninger. Adult reversal of cognitive phenotypes in neurodevelopmental disorders. J. Neurodev Disord. 1:150-157 2009

[4] Sondhi D. et al. Enhanced survival of the LINCL mouse following CLN2 gene transfer using the rh.10 rhesus macaque-derived adeno-associated virus vector. Molecular Therapapeutics 15:481-91 2006

[5] Guy et al. Reversal of neurological defects in a mouse model of Rett syndrome. Science 315:1143-7 2007

Gene findings from rare disorders have also provided clues to understanding common nervous system diseases—for example, the proteins that are mutated in rare forms of inherited Parkinson's disease and Alzheimer's disease also are involved in the pathology of the common non-familial forms of these diseases and are now targets for therapy development. However, we still do not know what causes most non-inherited cases of neurological disorders, whether or not there is an inherited type. What triggers most cases of Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), cerebral palsy, epilepsy, migraine, autism, chronic pain, and most other common neurological disorders remains largely unknown. Nor do we understand why some people recover from stroke or TBI much better than others. What we have learned provides plausible targets for developing treatments, and we are aggressively pursuing those opportunities; but better understanding of what triggers disease and drives progression of common neurological disorders is essential for developing cures. Understanding individual differences in how each person's genetic background shapes susceptibility to diseases and responses to environmental and behavioral influences on health of the brain is also just beginning, and this avenue of research holds considerable promise for personalizing prevention and treatment. From the perspective of diseases, the challenge for neuroscience is not only to apply what we do know quickly and effectively, but also that we do not yet know enough—we still confront a research problem, rather than a development or application problem.

The challenges of treating brain diseases are formidable—the complexity of the brain, its sensitivity to intervention, the variety of disorders, and the natural protective blood-brain barrier, which keeps out most potential drugs, to name a few. On the positive side, what we learn about the normal brain and about a single disease often benefits other disorders. Not only are some of the same misfolded proteins found in the brains of people with Parkinson's disease and Alzheimer's disease, but aberrations in how nerve cells handle other misfolded proteins are implicated in many different neurodegenerative disorders. The neurotransmitter dopamine is a key factor not only in Parkinson's disease, but also in drug addiction and in psychiatric disorders.

The protein mTor stands at a crossroads of fundamental cell regulatory systems and is involved in processes including memory and nerve fiber growth. mTor regulation has been at least tentatively implicated in diseases including tuberous sclerosis, neurofibromatosis, brain tumors, Alzheimer's disease, Parkinson's disease, Huntington's disease, fragile X syndrome, and autism, and several therapeutic strategies focused on mTor are under development.[6] These are just a few of the many examples of interconnections enhancing our understanding of diseases and between diseases and basic neuroscience.

Likewise, many therapeutic strategies may apply across several diseases. Deep brain stimulation was first proven effective for essential tremor, Parkinson's, and dystonia, and is now being investigated for possible use in Tourette syndrome, chronic pain, epilepsy, and psychiatric diseases, among others.[7] For many disorders, stem cell biology may yield replacements for lost cells, vehicles to deliver therapeutic agents to the brain, and tools to test drugs rapidly, as well as fundamental understanding of developmental processes. Methods to deliver therapeutic genes using gutted viruses that have a natural affinity for nerve cells may work for many diseases.[8] The more we understand the underlying biology of the normal brain and its diseases, the more we see common strategies.

THERAPY DEVELOPMENT RESEARCH

Physicians and scientists across academia and industry agree that support by the National Institutes of Health (NIH) for basic neuroscience research is essential for long-term progress against neurological diseases. The private sector supports little basic neuroscience research because the return on investment in any specific line of research is unpredictable; even results that constitute major scientific advances may not yield marketable intellectual property, and the time between a basic finding and a practical application can be decades long. However, basic

[6] Hoeffer C.A. and E. Klann. mTor signaling: At the crossroads of plasticity, memory, and disease. Trends in Neuroscience 33:67-75 2009
[7] Awan NR, Lozano A, and Hamani C. Deep brain stimulation: current and future perspectives. Neurosurgical Focus 29:E2 2010
[8] Foust KD et al. Intravascular AAV9 preferentially targets neonatal neurons and adult astrocytes. Nature Biotechnology 27:59-65, 2009

research alone is not enough, nor can we wait until we completely understand disease before developing better treatments. NIH must support therapy development research that the private sector will not undertake, for whatever reason. Rare diseases with small markets, bold therapeutic strategies that carry a high risk of failure or require long time horizons, new uses for existing drugs, and comparison of the effectiveness of available prevention strategies and treatments are among the many opportunities that the NIH is more likely than industry to move forward.

NIH's National Institute of Neurological Disorders and Stroke (NINDS) has a long history of therapy development. Over more than 40 years, the Anticonvulsant Screening Program has established more than 500 public private partnerships that contributed to advancing more than 50 drug candidates to clinical trials, resulting in 8 drugs approved by the Food and Drug Administration (FDA) for epilepsy and other conditions. For nearly as long, the Neural Prosthesis Program has pioneered the development of devices that restore lost nervous system function. Early developments included cochlear implants that restore useful hearing, and more recent advances include brain-computer interfaces that read control signals for computers and other devices directly from the brain. Similarly, the NINDS intramural program, working with the private sector in the final stages, developed the first enzyme replacement therapy for an inherited metabolic disorder, which was one of the very first biotechnology industry drug successes.

Driven by the increasing opportunities from basic neuroscience, NINDS has developed several new programs to speed therapy development. In 2003, NINDS established the Institute's most comprehensive program, the Cooperative Program in Translational Research, to support academic and small business investigator-initiated preclinical therapy development for any neurological disorder. Because the failure rate is high in therapy development, milestone-based funding allows investment with the understanding that NINDS will stop projects that are no longer making headway and shift funding to more promising opportunities. The "cooperative" in the program name reflects not only the need to bring together multiple types of expertise, but also cooperation across organizations. These projects can include investments by foundations,

academia, industry, and NINDS at various stages of the development process. Although the program is young, progress is encouraging; 6 candidate therapies have received FDA authorization to move into clinical trials. This and other NINDS translational programs complement and integrate with NIH-wide efforts, such as the NIH RAID (Rapid Access to Interventional Development) program and the Molecular Libraries high-throughput screening centers, in both of which NINDS plays a leading role.

Because of the scientific opportunity and the impact on patients and families, NINDS chose spinal muscular atrophy (SMA) to pilot a new approach to drug development. Several years ago, SMA was one of hundreds of poorly understood inherited disorders that affect the nervous system, and the outlook for developing treatments was bleak. The discovery of the gene defect that causes SMA gave way to a rational strategy for developing drug therapy. Through the SMA Project, experts from academia, industry, and the FDA developed a detailed drug development plan, and the project is implementing the plan through a "virtual pharma" organization that engages resources through organizations that serve industry drug development. The SMA Project has applied for patents on two promising novel drug candidates and is continuing with advanced preclinical safety testing toward the goal of completing certification for a clinical trial by the end of 2011.

Building on the SMA Project's approach, the NIH Blueprint for Neuroscience has launched a Grand Challenge on New Drugs for Diseases and Disorders of the Nervous System. The Blueprint is a framework for cooperative efforts among the 16 NIH Institutes, Centers, and Offices that support neuroscience research. This new initiative will support the development of drugs that have the potential to transform the treatment of neurological, psychiatric, and other nervous system diseases.

Because therapies for SMA and for several other neurological diseases may be ready for clinical testing in the next few years, NINDS is developing the Network of Excellence in Neuroscience Clinical Trials (NEXT) to improve the speed and effectiveness of early phase clinical testing of novel therapies, which present many logistical challenges. Through NEXT,

multiple clinical centers, a clinical coordinating center, and a data coordinating center will support testing of the most promising therapies. NEXT will test the most promising interventions, whether they arise from academia, foundations, or industry. The network will be especially important for rare disorders, including pediatric diseases, which often lack infrastructure for conducting clinical trials.

COLLABORATIONS AND COOPERATION

Neuroscience is inherently interdisciplinary, and collaboration is the norm. In the most recent issues of the premier basic neuroscience journals Neuron and Nature Neuroscience, for example, more than two-thirds of the research articles report cooperative research across different laboratories, departments, and institutions.[9] Even within laboratories, individual neuroscientists choose their training path to develop multiple areas of expertise, and laboratory leaders recruit post-doctoral scientists who bring new ideas, skills, and perspectives.

When the science dictates a cooperative approach, scientists will find a way, and the NIH stands ready to fund strong cooperative science. The NIH grant system encourages and enables cooperation among scientists through many programs. In addition to the flexibility of traditional research project (R01) grants, which are NIH's main investigator-initiated grant program, several types of grants encourage cooperation, from the multi-million dollar NIH Clinical Translational Science Awards (CTSAs), to multiple-principle investigator R01 grants, to small, rapid supplement programs. For example, in the translational realm, the NINDS Cooperative Program in Translational Research emphasizes the need for multi-disciplinary teams from a project's conception. Other NINDS programs with a strong translational emphasis include the Specialized Programs for Translational Research in Stroke (SPOTRIAS), the Morris K. Udall Centers for Excellence in Parkinson 's Disease, and the Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, which support multi-investigator centers that work together in networks across institutions, with common resources to foster sharing. The NINDS Collaborative Activities to Promote Translational Research (CAPTR) program is one example of a small but rapid

[9] See Neuron 67(6) September 23, 2010; Nature Neuroscience 13(9) September 2010

supplement program that catalyzes new collaborations as its primary objective. Three new NINDS collaborative initiatives are in development--one to increase the efficiency of initial testing of new therapies in patients, another to pursue identification and validation of biomarkers to facilitate drug discovery in Parkinson's disease, and a third to attack some of the most important challenges in epilepsy.

At the NIH itself, neuroscience intersects the missions of many Institutes and Centers just as the nervous system touches every part of the body. Many Institutes and Centers at the NIH support neuroscience research that may have implications for the missions of all. Interaction across the NIH occurs constantly, from Institute directors to the physicians and scientists who direct specific research programs. In the NIH Intramural Research Program, the Porter Neuroscience Center was designed from the ground up to foster interaction across basic and clinical neuroscience researchers regardless of their home Institute. In the NINDS extramural program, more than 80% of the currently active initiatives involve at least one other Institute. NINDS is collaborating with the National Institute of Arthritis and Musculoskeletal and Skin Diseases on neuromuscular diseases; the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) on hydrocephalus and rehabilitation for neurological disorders; the National Institute of Mental Health and the National Institute on Drug Abuse on NeuroAIDS; the National Institute of Biomedical Imaging and Bioengineering on improving deep brain stimulation technologies; the National Cancer Institute on brain tumors; the National Heart, Lung, and Blood Institute on stroke prevention and on major clinical trials; and the National Institute of Dental and Craniofacial Research on chronic pain, to cite just a few examples.

On a more formal level, the NIH Blueprint for Neuroscience brings together NIH Institutes to develop tools, support cross-cutting research, and take on challenges too big for any single Institute. Exciting new Blueprint initiatives include the Connectome project, which will chart for the first time the wiring map of the human brain; the Grand Challenge in Neurotherapeutics, which will set up a pipeline to move promising candidate drugs through preclinical development into early clinical trials; and a major effort to understand chronic pain. Beyond the specific

initiatives, the Blueprint fosters a spirit of cooperation across the NIH with regular meetings of Institute directors and more than a dozen active working groups.

Cooperation is also increasing in neuroscience between the public and private sector. As noted, NINDS and other NIH therapy development projects may arise from pilot work supported by foundations and often include academic-industry collaborations funded by the NIH. As the NIH reduces the risk of failure by moving projects through the challenging early stages of the therapy development pipeline, those that successfully meet their milestones can move on to final development in industry. NIH also catalyzes industry involvement in diseases of the brain through activities in the "precompetitive" sphere that provide tools and resources to increase the speed and efficiency for all public and private therapy development programs. For example, biomarkers that detect neurodegenerative disease early, before too many brain cells have died, and measure in months, rather than years, whether drugs are slowing the pace of disease progression could improve the effectiveness and reduce the cost of therapy development for many neurological disorders. A single company is unlikely to take on the task of developing biomarkers, but companies may join with others in a public-private partnership for this purpose. NIH supports investigator-initiated biomarkers development for many disorders. The Alzheimer's Disease Neuroimaging Initiative (ADNI) provides a new model of effective public-private cooperation to accelerate the pace of discovery in areas such as biomarkers. ADNI brings together expertise from the NIH and academia together with significant investment from the private sector to jointly tackle the biomarkers problem much more quickly and effectively than any one group could do alone. A new effort to develop biomarkers for Parkinson's disease will build on the lessons of the ADNI program.

NIH also cooperates in neuroscience research with other government agencies, including the DoD and VA. Both the DoD and VA have representatives on the National Advisory Neurological Disorders and Stroke Council, which oversees all NINDS activities. As one notable example of cooperation, in 2009 and 2010, researchers supported jointly by the VA and the NINDS published results from the first large, randomized, controlled clinical trial that compared the benefits and risks of deep brain stimulation and best medical therapy in a very

wide age range of Parkinson's patients.[10] [11] The trial also investigated the best sites in the brain for neurosurgeons to implant the stimulating electrodes. NINDS works very closely with the Department of Defense in CounterACT, an extensive NIH program to develop countermeasures against chemical threats, many of which target the nervous system. NINDS, VA, and DoD scientific program directors in spinal cord injury and neural prostheses routinely work together to ensure that the agencies' programs complement one another without unproductive overlap. For example, the Defense Advanced Research Projects Agency (DARPA) applied its expertise in high-tech devices to develop an advanced neuroprosthetic arm and hand. NINDS has now engaged our grantees with expertise in brain movement control circuits and neuroprosthetic interfaces to develop the best approach to controlling this arm, which DARPA is supplying to the NINDS investigators.

TRAUMATIC BRAIN INJURY

Unfortunately, war has long contributed to advances in neuroscience. Neurologists in the Russo-Japanese War of 1904-1905, for example, first mapped the visual representation in the cerebral cortex by observing the effects of penetrating bullet wounds in the brain.[12] TBI, the signature injury of today's wars, continues to inflict an immense burden on our military, which has spurred increased efforts in the DoD, VA, and the NIH. According to an Army Medical Surveillance Activity survey, 28,946 U.S. military personnel were diagnosed with a TBI in 2009 alone.[13] The civilian figures are equally alarming; each year about 1.7 million Americans are treated for TBI in hospitals and emergency rooms,[14] and this greatly underestimates the public health impact because people who are treated in physician's offices or outpatient facilities for mild TBI go uncounted in these statistics.

---

[10] Weaver F. et al. Best Medical Therapy versus Bilateral Deep Brain Stimulation for Patients with Advanced Parkinson's Disease: A Randomized Controlled Trial. JAMA 301:63-73 2009

[11] Follett et al. Pallidal versus Subthalamic Deep Brain Stimulation for Parkinson's Disease. New England Journal of Medicine 362:2077-91 2010

[12] Lanska DJ. Historical Perspective: Neurological Advances from Studies of War Injuries and Illnesses. Annals of Neurology 66:444-59 2009

[13] Defense and Veterans Brain Injury Center (DVBIC) website: http://www.dvbic.org/TBI-Numbers.aspx

[14] Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010. http://www.cdc.gov/traumaticbraininjury/statistics.html

NIH supports a wide spectrum of TBI research, from cellular and molecular studies to understand what goes wrong in animals through large scale clinical trials of treatment interventions in people. Although the immediate damage from severe TBI is often all too obvious, TBI triggers a cascade of damaging processes in the brain that continue long after the impact. Understanding those processes and stopping them is one major focus of ongoing research. For mild TBI, the problem is particularly challenging. We do not fully understand what causes damage, especially cumulative and long term effects from repeated mild TBI, and there is no reliable diagnostic to detect who has suffered an injury that should keep him from active duty or her from going back onto the playing field. NIH is funding research on improving brain imaging methods to detect the damage, on biomarkers in the blood, and on use of helmet impact monitors and systematic baseline and post-concussion neurospsychological testing of student athletes to better understand how physical forces affect the brain and to develop more sensitive tests that might be widely used.

More than 20 major clinical trials of interventions for TBI have failed, which has undoubtedly dissuaded many from taking on the challenge of developing interventions. Better understanding of the mechanisms that cause damage, more thorough preclinical testing in animals, and careful early phase trials to optimize therapies for larger trials are part of the answer. NINDS has developed the Neurological Emergency Treatment Trials Network (NETT), which brings together experts from emergency medicine, neurology, neurosurgery, and other disciplines to more efficiently recruit patients and to improve the quality of clinical trials of neurological emergencies, including TBI. The NETT is currently conducting a large, multi-center clinical trial of progesterone therapy for TBI, following encouraging results from extensive animal studies and a smaller clinical trial.

NIH has long collaborated with the DoD and the VA on TBI research, and those interactions have increased in recent years. The NINDS intramural research program has worked extensively with the VA and DoD on the long-term neuropsychological outcomes of TBI in veterans of the Vietnam War. This July the investigators reported on a multidisciplinary neurologic, cognitive,

behavioral, and brain imaging evaluation of 199 veterans some 30 to 35 years after their TBI.[15] More recently, the Center for Neuroscience and Regenerative Medicine (CNRM) was established as a collaborative intramural program among Walter Reed Army Medical Center, the National Naval Medical Center, and the NIH. In the CNRM, 26 NIH intramural investigators join with Uniformed Services University investigators on TBI projects that include both basic and clinical research. The NIH, Centers for Disease Control and Prevention, VA, DoD, and various other agencies also collaborate via the Federal Interagency TBI Research Network. Among the joint efforts are several productive scientific workshops on key issues for TBI research and treatment. Different workshops have focused on TBI classification, combination therapies, blast injury-induced TBI, integrated research on psychological health and TBI, common data elements for TBI research, field deployable diagnostics for mild TBI, and the impact of trauma disorders on military families and caregivers.

One notable example of efforts to follow up on issues raised at these workshops is a Grand Opportunity (GO) grant that the American Recovery and Reinvestment Act (ARRA) enabled the NINDS to fund. TBI can affect many parts of the brain in a variety of ways, and this heterogeneity has contributed to the lack of success in clinical trials because TBI in different parts of the brain and of different types may respond differently to treatment. The GO grant is addressing a consensus recommendation to develop novel approaches to classifying TBI that better predict response to treatment. The grant will also move forward on a joint proposal to implement standardized Common Data Elements (CDEs) that are suitable across a broad spectrum of clinical studies. The CDEs include data on demographics, brain imaging, outcome measures, biomarkers, and psychological health. Implementation of these common data elements will improve the quality and comparability of TBI studies funded by all agencies and make data from one study more accessible for answering other questions. In addition, the GO grant will develop performance indicators for comparative assessment of health care quality and effectiveness, which is essential given the current variability in care. This grant is just one

[15] Raymont V. et al. Correlates of posttraumatic epilepsy 35 years following combat brain injury. Neurology 75:224-9 2010

example of how NIH took advantage of the opportunity from ARRA funding to support research on TBI. Other ARRA-funded grants focus on a wide range of TBI issues, including mechanisms of damage, drug development, diagnostics, pediatric injury, and the role of brain plasticity in recovery.

Although TBI is the "signature" injury of Iraq and Afghanistan, it is certainly not the only intersection of neuroscience, military and civilian concerns. Indeed, TBI is itself not an isolated neurological problem, but rather has links to many other neurological disorders. Sports concussions, as well as studies in former military personnel, have raised the possibility that mild TBI can have long term consequences on neurodegeneration later in life. An NINDS scientific workshop on epilepsy last month highlighted post-traumatic epilepsy, a frequent consequence of TBI, as an opportune focus to begin the paradigm shift toward preventing the development of epilepsy, rather than merely suppressing seizures. Chronic pain is another problem that confronts military personnel with TBI and other traumatic injuries and is one of the most prevalent neurological problems in the civilian population. An NIH Blueprint Grant Challenge initiative is focusing on why acute pain sometimes, but not always, leads to the development of persistent chronic pain after an original injury has healed. Pain and its treatment can also lead to addiction. This Committee recently heard testimony on how neuroscience is coming to bear on that problem as well. Basic neuroscience advances in understanding brain plasticity may inform our understanding of the transition from acute to chronic pain, the development of addiction, and why some people recover so well from TBI and stroke, but others do not. NICHD's National Center for Medical Rehabilitation Research supports centers and other grants to apply the lessons from basic studies of brain plasticity and other insights from neuroscience to improving rehabilitation. The co-occurrence of TBI and PTSD is also, of course, an important issue. There are many more examples, but the message is simple – progress against each brain disease improves that outlook for others, and progress in basic neuroscience is essential for all.

CONCLUDING REMARKS

When progress against disease slows, it is usually due to a gap in our understanding of a very basic biological process. Progress in advancing the NINDS mission to reduce the burden of

disease rests upon our ability to manipulate the basic functional and structural characteristics of the nervous system. Discoveries about diseases often lead to the realization that basic science problems must be solved to successfully develop a treatment. In a sense, basic science provides the ammunition to defeat disorders of the nervous system. As we study diseases and test new treatments in clinical trials we are also building the arsenal of basic science knowledge that can be brought to bear on preserving and restoring brain health. The probability of success increases as the connections are strengthened between knowledge of basic biology, the disease mechanism, and the treatment effects on the disease mechanism. NINDS and the other NIH Institutes are working to narrow the gaps that separate these three key levels of knowledge.

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. The emphasis in my discussion today has been on the application of what we have learned from neuroscience to reducing the immense public health impact of TBI and the many other disorders of the nervous system. However, tomorrow's progress depends on taking on the fundamental challenges for neuroscience –how the brain works, how it develops, and what goes wrong in disease. We cannot predict precisely how the answers to those fundamental questions relate to disease, but we can predict that basic understanding will provide the foundation for progress against diseases of the nervous system.

Thank you for the opportunity to provide this information to you, and I will be happy to answer any questions.

Mr. KUCINICH. Thank you very much.
Dr. Kupersmith, you may proceed.

STATEMENT OF JOEL KUPERSMITH, M.D.

Dr. KUPERSMITH. I want to also thank the committee for inviting us, for having this hearing. I want to thank Dr. Insel and Dr. Koroshetz for their slide shows, which also act as a basis for what we have to say.

VA is one of the largest medical programs in the country, one of the largest research programs. And it includes close academic affiliations with major universities and medical schools.

We have over 3,400 researchers working on 2,300 projects and supported by approximately $1.9 billion in funding from all sources. We are widely supported by the Department of Defense and National Institutes of Health grants, our pharmacy coordinating center that is part of our nationwide clinical trials program, recently won the Baldridge Award, and has worked closely with NIH and DOD on projects.

Our collaborations with relative partners are extensive and essential to our advancement of research.

Our cutting-edge neuroscience research has extended from seminal studies on how memory is organized to the only evidence-based treatment for PTSD to Nobel Prize work on neuropeptides to a variety of genomic advances. I will highlight some of our findings and some of our research on PTSD, traumatic brain injury, spinal cord injuries and our work on the DEKA DARPA arm that was just mentioned.

We are a leader in PTSD research, currently supporting over 10 studies and spearheading the national dissemination of two evidence-based psychotherapies that we have proven to be most effective for PTSD, cognitive processing therapy and prolonged exposure therapy. We are also undertaking three large studies in the long-term assessment of PTSD and associated health conditions in Vietnam veterans. We have other studies which include genetic assessment of PTSD, genetic assessment of resilience to PTSD, treatment for sleep-related disturbances and strategies to engage veterans in early PTSD treatment.

Our research directly affects our PTSD guidelines and our guidelines are developed jointly with the Department of Defense. We have increased our research funding in traumatic brain injury, and at the beginning of fiscal year 2010, started three research centers dedicated to detecting and treating TBI. These include one that is going to specialize in PTSD and TBI and how to distinguish one in basic science, and one that is going to deal with other aspects of TBI.

VA is at the cutting edge of methods for detecting mild TBI through the use of biomarkers imaging and eye tracking assessments and is investigating, as I said, the links between TBI and PTSD and how to improve diagnosis of each.

We are also studying repetitive brain injuries combined with aging to determine whether these injuries can lead to neurodegenerative diseases. And there are some initial findings in that.

We have also and have always invested substantially in spinal cord injury research and recently started a spinal cord injury consortium to better address the needs of veterans with these conditions. One project involves combination therapy using bioscaffolds to implant stem cells with growth factors to repair and restore function. This approach, as Dr. Koroshetz intimated, is successful in rodents so far. But we are testing it in non-human primates. And it does hold promise to restore spinal cord function over the long haul.

Another group of studies we are doing is on functional electrical stimulation that applies low-level currents to nerves of spinal cord injured patients to stimulate muscle activity for movement of limbs, as well as for bladder function.

Now, our work on the new generation prosthetic arm, I think, is an example of mutual beneficial results of collaboration. This is the arm that Dr. Koroshetz mentioned. It was developed by DARPA. We are doing the clinical trials and optimization of it. And we have completed studies in 22 male and female veterans and military personnel and others.

We are testing the prototype, which has flexible socket design and innovative control features. And one of the important developments that has also been mentioned is that we will add the addition of brain computer interface technology. This is a group that is working at the Providence VA with a number of associated medical schools funded by us and also funded by the National Institute of Health. Right now, the DEKA arm is controlled by sensors that are in the feet. So it can only be used while sitting or standing, not while walking. But with this brain computer interface, we will enable individuals to walk and to command this prosthesis through thoughts in the brain.

Time does not permit me to discuss other VA neuroscience studies, but these are included in my written statement and I am happy to answer your questions. Thank you.

[The prepared statement of Dr. Kupersmith follows:]

STATEMENT OF
JOEL KUPERSMITH, M.D.
CHIEF RESEARCH AND DEVELOPMENT OFFICER
VETERANS HEALTH ADMINISTRATION
DEPARTMENT OF VETERANS AFFAIRS
BEFORE THE
DOMESTIC POLICY SUBCOMMITTEE,
OVERSIGHT AND GOVERNMENT REFORM
U.S. HOUSE OF REPRESENTATIVES

SEPTEMBER 29, 2010

Good morning Chairman Kucinich, Ranking Member Jordan, and Members of the Subcommittee. Thank you for inviting me to address the current state of neuroscience research, including efforts to discover and develop new treatments and diagnostic tools for brain and nervous system disorders. The Department of Veterans Affairs (VA) is committed to providing innovative, evidence-based approaches to clinical treatment that will provide our Veterans with the highest quality of care.

The rich history of more than 85 years of accomplishment by VA researchers has improved Veterans' lives and advanced the practice of medicine throughout the United States. VA has one of the largest medical research programs in the country, which includes close academic affiliations with major universities and medical schools nationwide. This year, nearly 3,400 VA researchers have worked on more than 2,300 studies and have been supported with nearly $1.9 billion in funding from all sources. We appreciate Congress' continued support of our research efforts. Today's dedicated VA researchers are focusing on traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), post-deployment health, women's health and a host of other issues key to ensuring the well-being of our Veterans.

VA benefits from supporting many clinical researchers who are able to translate the latest research findings into improved patient care, and who use their knowledge of patient care to develop further studies. Neuroscience has for many years been a major VA research endeavor. One of the Nobel Prizes awarded to VA investigators was to Dr. Andrew Schally for work on neuropeptides, which are hormone-like substances produced by the brain. His work developed a whole new realm of knowledge concerning the brain's control over body chemistry.

My testimony today will discuss VA's neuroscience research programs, including our work on the DEKA prototype of the next-generation prosthetic arm, and VA's commitment to collaborate with other Federal partners.

VA's Research Programs

VA's Office of Research and Development (ORD) within the Veterans Health Administration has long served as a leader in supporting novel treatment approaches. It supports pre-clinical, clinical and health systems research, and benefits greatly from being embedded in VA's comprehensive health care system with state-of-the art electronic medical records. VA ORD funds investigator-initiated research at levels that encourage VA's best scientists to participate in Veteran-centric research, within ORD's intramural research program. Seventy percent of these VA research scientists are also clinicians who provide care to Veterans. The majority of projects submitted for funding consideration originate with these clinician–scientists who treat Veterans in their clinical activities and who design their research proposals in a manner that reflects the medical issues they encounter while making treatment decisions.

Within our intramural research program, VA supports scientifically meritorious research with the goal of improving the health care of Veterans. A VA scientist first submits an application according to standard requirements for the specific funding mechanism that is scientifically peer-reviewed to evaluate significance, approach, research feasibility, and other factors. If deemed to be highly meritorious, the proposal would be recommended for funding. VA also supports the development and training of new scientists specifically through a career development program that provides salary and research support to investigators just beginning their research careers. Under the provisions of the program, the awardee works closely with scientific expert mentors to conduct research on important topics. Career development awardees, including clinicians and non-clinicians, often make long-term career commitments to VA by moving from career development mentored awards to become independent established VA scientists. Currently VA is funding career development awards in many neuroscientific and psychiatric topics, including Parkinson's disease, TBI, PTSD, stroke, rehabilitation, substance use disorders, sensory loss, and spinal cord injury.

VA promotes research across the range of disorders and diseases affecting Veterans, but I will highlight our neuroscience work in a few areas: PTSD, Substance Abuse, TBI, Spinal Cord Injuries and advanced prosthetics. Collaborations within the field of neuroscience between and among relevant partners are occurring and are crucial to help advance research in these areas. VA investigators are widely supported by Department of Defense (DoD) collaborations and National Institutes of Health (NIH) grants, as well as others, on a variety of research projects.

Post Traumatic Stress Disorder Treatment Research

VA has led efforts to discover new PTSD treatments including a large cooperative clinical research trial focused on Prolonged Exposure Therapy. There is a great need to understand the psychological and biological impact of trauma exposure in the Veteran population to most effectively understand, prevent, and treat PTSD and other adjustment disorders. Current research efforts in this area are looking to advance our understanding of these adjustment disorders. VA is currently supporting over 100 studies focused on PTSD at a cost of more than $27 million, including research focused on women Veterans and across different deployment eras such as Vietnam Veterans and those from operations in Iraq and Afghanistan. Many efforts are also directed to further understand the reactions when a traumatic event or experience such as combat occur, because knowledge of accompanying chemical and physiological changes may lead to better prevention and treatment. Some of this work includes modeling PTSD pre-clinically or tracking physiological reactions in laboratory settings. Overall, VA is spending more than $80 million to support mental health research.

There are a number of challenges VA and others face in treating PTSD. These challenges include an insufficient evidence base for treatment effectiveness and the complications presented by the Veteran population, who may have more severe comorbidity issues. In response, VA is spearheading the national dissemination of two evidence-based psychotherapies that have proven to be the most effective treatments for PTSD—Cognitive Processing Therapy and Prolonged Exposure Therapy. These treatments have also been validated by the Institute of Medicine report on treatment for PTSD that established these were the best treatments for PTSD.

VA research directly affects patient care through guidelines developed jointly with the DoD. VA's National Center for PTSD (NCPTSD) engages in collaborative research and educational projects with DoD, including the current revision of the Joint VA/DoD PTSD Clinical Practice Guideline. All of VA's Clinical Practice Guidelines are created jointly with DoD. Other NCPTSD collaborative projects with DoD include a VA/DoD Mental Health Guideline Tool Kit Development and Guideline Implementation strategy. In this effort, VA's NCPTSD is working with DoD to optimize the use of VA and DoD resources to develop the best mental health clinical practice guideline tool kits and guidelines to facilitate the use of evidence-based mental health care for Servicemembers and Veterans. VA currently has 29 ongoing DoD-funded research grants in this area.

Substance Use Disorder Research

VA has also recently partnered with the NIH to solicit research proposals in the area of comorbid substance use disorders and PTSD in the Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veteran population. This solicitation resulted in funding for new programs, including four supported by VA with a focus on smoking patterns following deployment, readjustment for members of the National Guard, issues unique to women Veterans, and how to improve treatment. A few examples of treatments currently being studied include an inexpensive medication to relieve trauma-related sleep disturbances, a novel drug in an early stage to alleviate PTSD symptoms, complementary and alternative therapies for PTSD, and strategies to engage Veterans in early PTSD treatment.

Traumatic Brain Injury (TBI)

In fiscal year (FY) 2010, VA is providing approximately $19 million for TBI research. In FY 2010, VA started two Centers of Excellence (one in Houston, TX and the other in Boston, MA) and one Research Enhancement Award Program (San Francisco, CA) that are devoted to detecting and treating TBI. VA is very invested in researching mild to severe TBI and the many issues and unknown consequences that accompany this prevalent injury.

VA is at the cutting edge in developing methods for detecting mild TBI (mTBI) through the use of biomarkers, imaging, and eyetracking assessments. Eyetracking studies are being tested for diagnoses of mTBI. Nerve fibers involved in eye movements are susceptible to the injuries that may occur from exposure to blast, and this type of research could be a helpful detection tool in theater.

Researchers are also developing innovative therapeutics for brain repair to improve care. In addition, VA is funding research involving Veterans with TBI and:

- Detecting risks for suicide in this population, which is at greater risk for mental health-related issues and suicide;
- Studying the prevalence of co-morbid balance and hearing impairments related to TBI, because the sensory organs of the ear are extremely vulnerable to blast injury, and the ears contribute to both hearing and balance;
- Studying the efficacy of tele-rehabilitation, because VA realizes that access to care is essential, and VA is leading the way in telemedicine and tele-rehabilitation research and care;
- Understanding and meeting the needs of caregivers of TBI patients, because caregivers of these Veterans experience increased levels of emotional stress, impacting the caregiver's mental and physical health;
- Improving "awakening" in TBI patients with disorders of consciousness, particularly for Veterans with severe TBI that may have long-term disorders of consciousness;
- Studying how the effects of repetitive brain injuries combined with aging, on long-term brain health and whether these injuries can lead to neuro-degenerative diseases; and
- Investigating the links between PTSD and TBI and how these conditions can be differentiated to improve diagnoses.

Some of VA's basic neuroscience research on TBI is directed toward clinical issues that affect our Veterans. The principal role that VA plays in treating Veterans with TBI is to improve their lives and health as much as possible and to support their reintegration to society. VA research is supporting several projects in this area:

- A project to study the development of molecules with neurotrophic properties that can pass the blood-brain barrier to mediate brain repair after TBI.
- A project to study the effects of locomotor training on closed-head TBI-induced disabilities. Currently, there is not a clear understanding of the neurobiology of long-term cognitive, motor, and behavioral disabilities induced by TBI. Rehabilitation can enhance the recovery of these abilities, and this study will investigate the mechanism and impact of therapeutic locomotor training to significantly decrease the magnitude of TBI-induced disabilities.
- A collaborative project with the National Naval Medical Center to investigate a possible causal mechanism of TBI on PTSD using a rat model of mTBI to determine the neurobiological consequences of a blast injury.

Spinal Cord Injuries

VA is investing substantially in Spinal Cord Injury (SCI) research. For example, VA recently started an SCI consortium, led by some of VA's best researchers, to better address the needs of Veterans with these conditions. The Consortium's studies include regeneration genetics, imaging methods on regeneration and plasticity of nerves after injury, and the testing of combination therapies in non-human primate models of SCI.

Combination therapy is a major project being tested by VA researchers who are a part of the Consortium. Combination therapy uses "scaffolding" such as cartilage to plant stem cells to generate and grow spinal cells and repair the injury. This therapy is only in the phase of testing involving non-human primates. Another therapy being developed by VA researchers is Functional Electrical Stimulation (FES). FES applies low-level electrical currents to either generate or suppress activity in the nervous system. FES can stimulate physical or bodily functions to produce and control the movement of otherwise paralyzed limbs for standing and hand-grasping, activate visceral bodily functions such as bladder control or respiration, create perceptions such as skin sensitivity, help stop experiences such as pain or spasm, and facilitate natural recovery and accelerate motor relearning.

VA's FES Consortium and Center of Excellence (CoE) on FES is working in collaboration with the private educational institution of Case Western Reserve University

(CWRU) in Cleveland, Ohio, and the public hospital system of CWRU's Metro Health Medical Center. These researchers, engineers, and clinicians work to develop technological solutions, such as FES, that improve the quality of life of individuals with neurological or muscular skeletal impairments. This is a prime example of public-private collaborations resulting in promising research.

Another example of a collaborative effort is NIH's National Institute on Drug Abuse (NIDA) and VA's partnership on spinal cord injuries (SCI). Many military personnel returning from Iraq and Afghanistan experience pain. Pain is often co-prevalent with PTSD, persistent post-concussive syndrome, and sleep disorders; it interferes with daily functioning and adversely affects quality of life. Inadequate treatment opens the gate to analgesic misuse and substance use disorders. A prominent VA researcher is working on chronic pain conditions and how they relate to the abnormal activity of sodium channels. Sodium channels are an integral part of the nervous system and in transmitting messages. The normal activity of these channels can be disrupted following injury to the nervous system (e.g. spinal cord injury or multiple sclerosis), or to the pain receptors themselves (burns), leading to chronic pain. The researcher and his team are currently examining ways to alter the activity of the sodium channels and to develop novel non-opiate methods to treat chronic pain following injury and disease.

Another recent advance in the field of pain research involving VA indicates that an assessment called brain fMRI (functional magnetic resonance imaging) has the ability to determine functional activity-based measures of pain-related processes, the analgesic effect, and potentially the states of pain. Brain fMRI is non-evasive, uses no radiation and offers high quality results. This collaborative effort with NIDA fosters interactive and innovative partnerships between NIH imagers, investigators and VA pain clinicians. These teams unite the expertise of each Federal agency to achieve the following aims:

1) Detect, characterize and validate "fingerprints of pain" using imaging data in combination with self-report scales and other phenotypes of pain;

2) Harmonize the assessment of the effectiveness of various types of pain management techniques used at VA; and

3) Create a pain registry for comparative effectiveness research and to confront the complex cascade of the many associated conditions that Veterans with chronic pain have.

This approach, which combines the direct observation of bedside care and work in the laboratory, will enable a positive transformation of current advances in the science of pain and pain management into objective evaluation and prediction of drug responses and disease progression, development of novel non-opiate medication and intervention, and better patient care, matched to the needs of the individual. As the research evolves, these labors will help develop innovative concepts for the next stage of evidence-based studies and pave the way for new partnerships that share common interest and resources between the NIDA and VA.

VA Clinical Research of DEKA Arm
(Funded by DARPA with prototypes being produced by DEKA Research and Development Corporation)

The DEKA Arm initiative is an excellent example of the mutually beneficial results that occur when VA and DoD work collaboratively to better serve those who have lost arms in combat. This initiative, coordinated by VA in Providence, Rhode Island, consists of three VA sites and one DoD site, the Center for the Intrepid at Brooke Army Medical Center in San Antonio, TX. Twenty-one male and female research participants have completed the study, including Veterans and Servicemembers.

The Next-Generation Defense Advanced Research Projects Agency (DARPA) Prosthetic Arm System incorporates major technological advances such as flexible socket design and innovative control features, hardware, and software that together enable enhanced functionality that promises to surpass any currently available prosthetic device. Ongoing results of this VA clinical research are contributing to the design efforts leading to the optimization of a revised version of the Next-Generation DARPA Prosthetic Arm System. VA will employ a similar design to conduct usability research on the revised arm system. The expectation is that the results of these efforts will lead to commercialization of a refined, highly usable product. The DEKA Arms are

currently only being tested in research laboratories and are not yet available for Veterans to take home for use.

VA is planning additional follow-on studies in upper extremity prosthetics, particularly take-home trials pending the availability of arms. This is the final step in the research process prior to routine clinical provision of the arms to our Veterans and active duty Servicemembers. If the research is successful and the arms become commercially available, this will allow Veterans to obtain DEKA Arms through VA's Prosthetic and Sensory Aids Service in the VA Amputation System of Care. VA is also looking at the transition of these advanced prosthetics arms to additional applications, such as mounting on wheelchairs for Veterans with high-level spinal cord injuries, enabling the Veteran to control the arms to increase independence in activities of daily living. These innovations would not be possible without the collaboration of DoD and other Federal partners.

Brain Computer Interface

Another exciting development is the brain computer interface, also known as "BrainGate" research. This is an important effort that addresses questions of how Veterans with physical limitations can still engage the physical environment with their minds. For example, Veterans often use a joystick to control a powered wheelchair, but if they lose the use of their hands, brain computer interface research can help identify new methods to improve functionality. The concept behind this technology is that we can record the activity of single cells in the brain and then use computers to "decode" the neural signals into "commands". These commands could potentially be used to control mechanisms such as a computer mouse and its buttons or a wheelchair with a joystick.

Researchers are also looking at this technology for use by Veterans with high level spinal cord injuries or neurodegenerative conditions such as Amytrophic Lateral Sclerosis, where the Veteran can no longer use his or her arms and hands. Research has already demonstrated the feasibility of this technology to allow users to control computers and wheelchairs directly from signals in the brain. VA is just beginning a research study to see if a brain computer interface can control advanced prosthetic

arms. The DEKA arm is currently controlled by sensors mounted on the feet, so it can only be used when sitting or standing and not while walking. The hope is that in the future BrainGate technology will be available for controlling advanced prosthetic arms.

Artificial Retinal Implant

Another successful collaboration between VA and private facilities involves a project receiving support from Harvard Medical School, the Massachusetts Institute of Technology and Cornell University (Nanofabrication Lab) and VA's CoE on Innovative Visual Rehabilitation, which is working on an artificial retinal implant. This project is trying to develop a microelectronic retinal implant to restore functional vision to Veterans with certain forms of blindness, including age-related macular degeneration, which is the leading cause of blindness within the industrialized world and among U.S. Veterans; retinitis pigmentosa, which is the leading cause of inherited blindness in the world; and also retinal damage that accidentally occurs from exposure to range-finders, which are in widespread use by the military.

Recent accomplishments that will lead to development of a device for human implantation include:

- Successful animal implantation of a device which implemented new key features in the ability to wirelessly monitor the status of each electrode and its tissue interface, improving robustness of bi-directional communication to the implant;
- Detailed characterization of the electrochemical properties and charge-injection behavior of the iridium oxide electrodes over time in model body fluids at body temperature;
- New transmitter circuits for data telemetry, which deliver data wirelessly via an inductive link to the retinal prostheses; and
- A new system that may be used to extract visual features from the Veteran's environment that would be suitable for transmission to a retinal implant device.

Federal Collaborations

VA has extensive relationships with our Federal partners, particularly NIH and DoD, to ensure Veterans receive the most from research. VA's research partnership

with NIH is exemplified by the Deep Brain Stimulation (DBS) Study which VA is conducting in collaboration with NIH's National Institute of Neurological Disorders and Stroke. VA is proud to partner with NIH on this ongoing study which is the largest trial of its kind to date. This and other ground-breaking research on Parkinson's disease ensures that we provide the best care possible for Veterans with this common debilitating disease. VA cares for about 40,000 Veterans with Parkinson's disease. DBS is often recommended for people who no longer respond well to medication alone. In DBS, surgeons implant electrodes in the brain and run thin wires under the skin to a pacemaker-like device. Electrical pulses from the battery-operated device jam the brain signals that cause motor symptoms such as stiffness and tremors. Thousands of Americans have seen successful results from DBS, but questions have remained about which of two stimulation site in the brain yields better outcomes. The latest DBS study results, recently published in the New England Journal of Medicine, show that DBS is equally effective at either of two sites in the brain.

Since FY 2007, more than 80 VA researchers have been receiving over $70 million in funding on issues of importance to both DoD and VA. These issues include PTSD, TBI, prosthetics, rehabilitation, psychological health and well-being for military personnel and families, deployment-related injuries and illnesses, and polytrauma. VA and DoD also partner on several Centers of Excellence and serve on interagency committees related to research. VA and DoD share a common vision in studying military personnel from pre-deployment to post-deployment to better understand the population we serve. VA and DoD collaborate through every phase of research program management from planning new and targeted initiatives, collaborating on active research studies, sharing findings, reviewing portfolios and setting priorities. VA also participates actively on DoD Joint Program Committees for PTSD and TBI, and VA and DoD experts serve on scientific peer review panels for each Department.

VA partners with the DoD on the Defense Center of Excellence (DCoE) for Psychological Health and Traumatic Brain Injury. VA has co-located two VA-DoD liaisons and subject matter experts at DCoE, one for psychological health and another for traumatic brain injury. VA and DCoE jointly chair the Substance Abuse and Mental Health Services Administration (SAMHSA)-sponsored Federal Partners Reintegration

Work Group, which works to ensure improved transition of Veterans from active duty into civilian life, reducing stigma associated with mental disorders and other supportive activities.

Conclusion

Thank you again for this opportunity to speak about VA's work to better understand and treat neurologic and psychiatric diseases and injuries, specifically PTSD, substance use disorders and TBI. In our ongoing quest to deliver the latest in treatment, technology, and rehabilitation services to America's Veterans, VA supports robust basic, clinical and systems research efforts to develop an evidence-base for new approaches to health care. VA is proud to spearhead innovative research that improves the lives of Veterans, their families and caregivers, and ultimately many others in the Nation who benefit from VA's research advancements. I am prepared to answer any questions the Subcommittee might have.

Mr. KUCINICH. Dr. Rauch, you may proceed.

STATEMENT OF TERRY M. RAUCH, PH.D.

Mr. RAUCH. Mr. Chairman, before I give my statement, I would like to thank Mr. Kennedy for his hard work in this area. This old retired soldier very much appreciates your effort in this critical area.

Mr. Chairman, members of the committee, thank you for the opportunity to discuss Department of Defense research efforts to advance our understanding of neurological and psychological trauma. We greatly appreciate the committee's support of our efforts to discover and develop diagnostic treatment and prevention strategies to help the many brave men and women who have been afflicted with these debilitating disorders.

Mr. Chairman, without a doubt, the devastating nature of neurological and psychological trauma is one of the most difficult challenges we face with respect to research and development and translation of discoveries in clinical care. The central nervous system allows us to interact with the world around us. Therefore, any neurological or psychological injury can be devastating, not only to the service member but also to the family members as well.

Psychological trauma in many cases has proven responsive to various therapies, but it remains a difficult challenge to identify and effectively treat. Recovery from psychological trauma is often complicated by co-occurring physical injury, depression, substance abuse and the threat of suicide. Even mild cases of neurological and psychological trauma can have devastating effects on lives, careers and families.

The Department of Defense has developed a comprehensive research and development program for the study of neurotrauma and psychological health. The programs focus on basic mechanisms of disease and applied and clinical research that address prevention, diagnosis, treatment and rehab. This research and development is conducted by investigators within DOD, within the VA, within NIH and within leading academic institutions and also in industry partners.

Psychological trauma has posed a significant threat to service members. During Operations Iraqi Freedom, now Operation New Dawn, and Enduring Freedom, an estimated 20 to 40 percent of service members experienced behavioral health problems post-deployment, most often PTSD, depression, and interpersonal conflicts. Studies have also shown evidence of increased strain on families.

Our highest priority in neurotrauma research is the diagnosis of TBI, specifically mild TBI. While moderate and severe TBI are relatively straightforward, to diagnose mild TBI can be difficult to assess, particularly if the service member has an injury that wasn't witnessed. Our goal in diagnostics has been to identify the unique biological effects of TBI and to leverage that knowledge to identify or develop more effective, objective diagnostic tools that will determine the presence and severity of brain injury.

To meet this challenge, we have funded research on more than 60 different technologies over the past 4 years. These include blood biomarkers of TBI, identifying unique electrical paterns of the

brain, indicative of injury and the severity of that injury, and more valid and reliable neurocognitive diagnositc tests.

With regard to treatment and rehab research on neurotrauma, we currently sponsor more than 70 projbects investigating drug and drug combinations, nutritional compounds with therapeutic potential, cell and gene therapies used in regenerative medicine, deep brain stimulation and rehab methods and devices.

We sponsor a significant amount of work to better understand neurobiological basis of PTSD. Significant research is underway to discover objective techniques to distinguish between PTSD and TBI. These efforts are focused on neuroimaging techniques, as well as biomarkers specific to PTSD and mild TBI.

We have also invested significantly in research to identify the most promising drugs to treat various PTSD symptoms and to use in combination with different psychtherapies.

Last, suicide is a significant public health problem. It has been identified as the third leading cause of death of young people and the eleventh overall leading cause of death in the U.S. population. Until recently, military suicide rates have been significantly lower than general population rates. However, in 2004, military suicide rates began to climb, and today, exceed the age-adjusted civilian rate.

In order to better understand the factors related to suicide, the DOD and NIH are invoolved in an ongoing collaboration, as my colleagues described before, to conduct the largest scale study of suicide in the military. The project is the largest epidemiologic study of mental health, psychological resilience, suicide risk, suicide-related behaviors and suicide deaths in the U.S. Army.

Drug, including prescription drugs and alcohol abuse, is a significant health problem in the military. Almost 30 percent of the Army's suicide deaths from 2003 to 2009 and more than 45 percent of the non-fatal suicide behavior from 2005 to 2009 involved the use of drugs or alcohol. Increased prescription use among the military has led to heightened concern with overdoses. We have sponsored a significant amount of substance abuse research that includes epidemiologic studies as well as studies investigating prevention and treatment interventions. Further epidemiologic research is needed to accurately characterize drug use and mis-use to include risk factors and to identify potential barriers to treatment-seeking behavior.

Mr. Chairman, the Department of Defense continues to perform and manage exceptional medical research and development for the population that demands and deserves the finest care available. I am proud to be here today to represent the men and women who conduct these programs. And I thank them for their service. I thank you, Mr. Chairman, for the opportunity to be with you today and I look forward to your questions.

[The prepared statement of Mr. Rauch follows:]

STATEMENT

BY

TERRY M. RAUCH, PH.D.

DIRECTOR, DEFENSE MEDICAL RESEARCH AND DEVELOPMENT PROGRAM
OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

REGARDING

THE CURRENT STATE OF NEUROSCIENCE RESEARCH IN THE DEPARTMENT OF DEFENSE

BEFORE THE

DOMESTIC POLICY SUBCOMMITTEE OF THE HOUSE OVERSIGHT AND GOVERNMENT REFORM COMMITTEE

SEPTEMBER 29, 2010

Mr. Chairman and members of the Committee, thank you for the opportunity to discuss the efforts of the Department of Defense (DoD) to advance our understanding of neurological and psychological trauma. We greatly appreciate Congress' strong support of our efforts to discover and develop treatments to help the many brave men and women, who have been afflicted with these debilitating disorders.

The devastating nature of neurological and psychological trauma is undoubtedly one of the most difficult challenges we face with respect to research, development and translation of discoveries to clinical care. The central nervous system allows us to interact with the world around us; therefore any neurological or psychological injury can be devastating not just to the injured Service member but to family members, as well.

Psychological trauma, in many cases, has proven responsive to various therapies, but it remains a difficult challenge to identify and effectively treat. Recovery from psychological trauma is often complicated by co-occurring physical injury, depression, substance abuse, and the threat of suicide. Even "mild" cases of neurological and psychological trauma can have devastating effects on lives, careers and families.

My testimony today will focus on the areas of neurotrauma, including traumatic brain injury (TBI), and psychological trauma, which includes posttraumatic stress disorder (PTSD), suicide, and substance abuse.

From January 2000 until May 2010, 178,876 cases of TBI (both combat and non-combat) were diagnosed in Service members. Of those, 3,175 were penetrating, 1,891 were severe, 30,893 were moderate and 137,328 (or 77%) were mild. The remaining TBI cases (5,589) were not classifiable.

Mild TBI probably is under-diagnosed. One reason is the co-incidence of TBI with other trauma (polytrauma), as in blast injuries. In addition, some Service members do not recognize they have been injured until well after an event, and some do not want to be removed from their teams. Updated guidelines for mandatory screening and follow-up after an event are outlined in the Directive-Type Memorandum 09-033 "Policy Guidance for the Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting." Our ability to diagnose TBI is improving; however, TBI and post-concussion disorder can co-occur with psychological trauma, most commonly PTSD, which complicates diagnosis and recovery.

Psychological trauma has posed a significant threat to Service members during Operations Iraqi Freedom (OIF) [now Operation New Dawn (OND] and Enduring Freedom (OEF). Multiple deployments, intense combat experiences and limited time between deployments, all common to OIF/OND/OEF, are associated with behavioral health problems, substance abuse and risky behaviors. An estimated 20 to 40 percent of Service members experience behavioral health problems post-deployment, most often PTSD, depression, and interpersonal conflict. Studies have also shown evidence of increased strain on families.

DoD Research Overview

The Department of Defense has developed comprehensive research and development programs for the study of neurotrauma and psychological health. The programs focus on basic mechanisms of disease, and applied and clinical research that address prevention, diagnosis, treatment and rehabilitation.

Within DoD, the Defense Health Program (DHP) funds the majority of research and development on prevention and treatment of neurological and psychological trauma. This research and development is conducted by investigators in the DoD, the Department of Veterans Affairs (VA), the National Institutes of Health (NIH), leading academic institutions, and industry partners.

Neurotrauma Research

While our highest priority objective currently is the diagnosis of TBI, and specifically mild TBI, we have only a modest understanding of the biology and progression of TBI. Efforts are underway to study the natural history of TBI in humans. For example, an academic consortium is examining mild TBI from the subcellular to whole body levels. It is investigating improved, standardized methods for assessing neurological status and outcome. The combination of TBI with polytrauma is a significant issue. Several academic and DoD labs are working to develop blast and impact TBI animal models that include hemorrhage as a model for polytrauma.

Prevention

Knowledge leading to improved preventive measures, such as improved body armor, will emerge from research efforts. DoD is studying the effects of blast upon the brain and body to include the complex interplay between neurotrauma and trauma to other organs. Improved animal models and human computational models of brain and polytrauma will allow the development of improved protective systems. The primary objective of the Helmet Mounted Sensor System program, led by the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) program, is to document head

impact and blast exposures in the field to provide data for the development of more objective head injury screening tools. These impact and exposure data will provide data for the Next Generation Combat Helmet.

Diagnosis

There have been no major, recent changes in rating scales of TBI since the development of the Glasgow Coma Scale in 1974, and the regular use of computed tomography (CT) and magnetic resonance imaging (MRI) in the 1980s. The need for improved diagnostics is possibly the most critical, considering the need for an objective diagnosis of mild TBI. While moderate and severe TBI are relatively straight forward to diagnose based on clinical definitions and the Glasgow Coma scale, mild TBI remains a challenge. Mild TBI can be difficult to assess if the Service member has an injury that was not witnessed. Our goal in diagnostics has been to identify the unique biological effects of TBI and to leverage that knowledge to identify or develop more effective objective diagnostic tools that will determine the presence and severity of brain injury.

To meet this challenge, we have funded research on more than 60 different technologies over the past four years. These include blood biomarkers of TBI that often are derived from parts of damaged neurons; electroencephalography – identifying electrical patterns unique to injury and indicative of severity; smooth pursuit eye tracking, which measures attention, vision and movement networks within the brain; neurocognitive assessment tests that assess memory and decision making; and other laboratory tests of brain function. The Biomarker Assessment for Neurotrauma Diagnosis and Improved Triage System (BANDITS) program aims to provide a panel of biomarkers

(i.e.,, proteins released into the blood by damaged CNS cells) that can be assessed by a medic with a handheld device. This program will enter its pivotal clinical trial in fiscal year 2011. Mild TBI will require multiple diagnostic modalities.

Medical imaging technologies have a huge role in defining and diagnosing TBI. Diffusion Tensor Imaging (DTI) and Diffusion Spectroscopic Imaging (DSI) are being studied by several teams. Refining these techniques will allow us to visualize damage to nerve tracts within the brain and spinal cord. Scientists at Landstuhl Regional Medical Center aim to determine whether blast induced TBI patients demonstrate unique patterns of brain injury in comparison to impact TBI. Other DoD studies seek to identify the optimal selection of tools for diagnosing and following TBI. These neuroimaging techniques will allow visualization of detailed structural and functional effects of TBI, as well as the effects of various treatments and rehabilitation efforts. Up to 40 percent of combat TBI patients cannot be studied in an MRI machine, due to retained metal fragments from blast injuries, innovative approaches to structural and functional imaging are also being studied.

Treatment and Rehabilitation

To date, the U.S. Food and Drug Administration has not approved any drugs for use as a treatment for TBI. This is not due to a lack of effort. In recent times, no fewer than 27 clinical trials have tried, but failed, to identify a safe and effective therapy for TBI. The DHP currently sponsors a neurotherapeutics portfolio of more than 70 projects investigating:

- Twenty-five drugs and drug combinations;

- Nutriceuticals (nutritional agents with therapeutic potential, such as Omega-3 fatty acids which are part of neuronal membranes);
- Cell and gene therapies (regenerative medicine);
- Neuroprostheses and neuromodulators (such as deep brain stimulation and direct current electrical stimulation); and
- Rehabilitation methods and devices.

Multifunctional agents that act in more than one part of a physiological process show promise. These agents include statins (currently for lowering cholesterol), erythropoietin, minocycline and progesterone, among others. DoD has collaborated with industry on the development of the drug NNZ-2566, a naturally occurring neuroprotectant, derived from Insulin-like Growth Factor 1. In addition, we are also funding clinical trials of perfluorocarbon oxygen delivery liquids with possible neuroprotective benefit.

Currently, the only promising therapy for TBI in large clinical trials is progesterone and NNZ 2566. The phase III progesterone trial is entitled "Progesterone for Traumatic Brain Injury (ProTECT III)." The civilian partners are funded by the NIH with numerous nationally recognized hospitals. DoD has been involved with the discussions and coordination of the study that is planned to be conducted at the San Antonio Military Medical Center. Meanwhile, DoD and civilian scientists have moved NNZ 2566 to phase II (assessment of effectiveness and safety in a group of 100-300 patients) studies.

Collaborations

Several examples of our collaborations with academia, industry and other government agencies have been stated above. Our research program managers collaborate with their VA and NIH counterparts on a regular basis and serve on one another's research review panels as well as on our Joint Program Committees.

The Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) is charged with the dissemination of emerging knowledge from research, as well as the assessment and facilitation of preventive efforts, diagnosis, therapies, rehabilitation and reintegration.

The DCoE is very active in developing collaborative projects, such as the Common Data Elements Project, which is an effort co-sponsored by DoD, NIH, VA, and the Department of Education. This project brought together more than 150 leading subject matter experts from the Federal government, academia, and industry to develop recommendations for standard definitions, metrics, and procedures for use in TBI and psychological health research. This increased standardization will help with the performance and comparison of research results.

DoD is working directly with NIH to develop a comprehensive comparative effectiveness research program on the diagnosis, treatment, and outcomes of TBI. All of this cooperation is critical, considering the potential for many diagnostic modalities and therapies to be translated to clinical use in the next five to 10 years. In addition, DoD funds nearly 350 VA and VA-affiliated investigators who perform medical research including TBI and psychological health research.

In summary, the neurotrauma community agrees that the most promising approach to treatment and rehabilitation will not be through any single therapy but rather through combinations of drugs, drugs and cells, or drugs and DNA. Neuroprosthetics might allow recovery of some functions, but it is only by healing the brain and spinal cord that we will definitively treat neurotrauma.

Psychological Health Research- PTSD

I would like to now focus on psychological health. PTSD is a complex disorder associated with significant co-occurrence with other behavioral health issues, disability, and impairment of daily living resulting from exposure to a traumatic event. If ineffectively treated, PTSD can develop into a chronic, long-term condition with marked vocational and interpersonal impairment. PTSD symptoms include re-experiencing the traumatic event in some way, avoidance of reminders of the event, and hyperarousal or agitation. According to the National Center for PTSD, studies to date suggest that 10 to 18 percent of Service members serving in OEF/OND/OIF have probable PTSD following deployment.

Because of the complex interaction of physiological, cognitive, and behavioral factors involved in this disease, it has been difficult to identify potential diagnostic and therapeutic candidates. Over the past five years, DoD investment in PTSD and behavioral health research has been important to developing solutions to these problems; however, a significant amount of research remains to be done to close gaps in knowledge.

Psychological trauma is not unique to the military, but, there are aspects of combat-related psychological trauma, including environmental, cultural and relationship

factors that are unique to the military. Differences in combat-related PTSD and other traumas are consistent with research that has shown that veterans tend to have poorer treatment response and more severe and chronic posttraumatic symptoms than do civilian counterparts. Unfortunately, existing medications for PTSD have limited ability to decrease symptoms. Research indicates that the medications are modestly effective (less than 40 percent). Although there are several evidence-based psychotherapies for PTSD symptoms, they are less than 50 percent effective, and these therapies have not all been validated for treating combat-related PTSD. Current treatments are not designed to target commonly experienced co-occurring issues such as depression, substance abuse, and sleep disturbance.

The Defense Health Program (DHP) supports a significant portion of DoD's effort to better understand the neurobiological basis of PTSD. This investment includes developing and using validated animal models of PTSD that parallel human combat-related PTSD to understand the complex interactions of mechanisms and processes that lead to the development of PTSD symptoms. This animal research is being done in parallel with human imaging and molecular biology studies in order to provide a better understanding of the underlying mechanisms of PTSD.

Significant research is underway to discover objective techniques to distinguish between PTSD and mild TBI. These efforts are focused on neuroimaging techniques as well as biomarkers specific to PTSD and mild TBI. VA researchers are leading the efforts in developing and validating biomarkers to distinguish between PTSD and mild TBI.

The DHP has also invested significantly in research to identify the most promising drugs to treat various PTSD symptoms and to use in combination with psychotherapy. This includes an evaluation of clinical cognitive and behavioral therapies to determine which are the most effective in treating PTSD, including traditional cognitive therapies (e.g., Cognitive Behavior Therapy, Cognitive Processing Therapy, Prolonged Exposure Therapy), as well as non-traditional therapies such as acupuncture, mindfulness, yoga, and animal-assisted therapies. Rigorous evaluation of these therapies is critical to ensure that they are safe and effective.

Telepsychiatry is being investigated as a method to enhance accessibility of psychotherapy for Service members in remote locations and to reduce stigma associated with receiving help. Other investigators are examining the use of virtual reality technology to enhance therapy effectiveness.

Future work in the area of PTSD must focus on research gaps that include therapies for PTSD with co-occurring problems and treatments for refractory PTSD. Continued research is also required to enhance diagnostic and treatment efficacy so that our Service members can return to previous levels of functionality and quality of life.

Suicide

Suicide is a significant public health problem that has been identified as the third leading cause of death in young people and the eleventh overall leading cause of death in the U.S. population. Until recently, military suicide rates have been significantly lower than general population rates. However, in 2004, Army suicide rates began to climb, and in 2008, the Army rate exceeded the age-adjusted civilian rate.

In 2008, the Armed Forces Medical Examiner reported that 50 percent of all fatalities in DoD could be accounted for by the combined total of accidents and suicides. Suicides outnumbered combat deaths for the first time since 2003. Between 2001 and 2007, suicide rates for both the Army and the Marine Corps have steadily increased. Navy and Air Force suicide rates have slightly increased; however, it is not clear if this is the beginning of an upward trend. Of the Army suicides that occurred between 2005 and 2009, 80 percent occurred within the U.S. and 17 percent were in theater. The most common stressors associated with suicides included relationship issues (55.8%), military/work (57.4 %), physical health (23.2 %) and substance abuse (16.7 %).

There are several hypotheses regarding the increase in Army suicides. These range from increased stress due to multiple deployments to changes in demographics with more new enlistees receiving waivers for pre-existing conditions. Other hypotheses include factors related to the effects of substance misuse and abuse (alcohol, illicit drugs, and prescription medications), quality of care issues, and stigma associated with seeking help.

Between 2001 and 2009, 14.5 percent of suicides occurred among individuals who had received inpatient care and 41 percent who had received outpatient care for a mental health diagnosis. The current state of care management and follow-up treatment guidelines needs improvement.

Although suicide prevention training programs, material, and other prevention efforts are available, there is a lack of evidence demonstrating the effectiveness of these programs. Programs such as *Beyond the Front,* the *A.C.E.* ("Ask", "Care", and "Escort") *Gatekeeper* intervention, and *Chain Teaching* are widely disseminated. However, there

is a lack of research evaluating program effectiveness to increase recognition of individuals who may need help, decrease suicide behaviors, or prevent suicide. Evaluation of suicide prevention efforts is critical.

In 2009, DoD led a series of workshops with leading experts in suicide and military stakeholders to determine the state of science of suicide prevention research. The workshops led to the development of a research strategy in four focused areas: Suicide risk screening and assessment; Universal prevention training; Indicated interventions to manage suicide behavior; and Recommendations for revisions to the Post Deployment Health Assessment and Post Deployment Health Reassessment.

The suicide prevention research program involves extensive collaboration among DoD, NIH, VA, academia, and national organizations such as the American Foundation for Suicide Prevention and the American Association for Suicidology Research. In order to better understand the factors related to suicide, the DoD and NIH are involved in an ongoing collaboration to conduct the largest scale study of suicide in the military; the project, "Army Study to Assess Risk and Resilience in Service members" (Army STARRS) is the largest epidemiologic study of mental health, psychological resilience, suicide risk, suicide-related behaviors, and suicide deaths in the U.S.

Despite the current investment in suicide prevention research, there is much more work to be done in this area. The strategic research plan calls for further research that comprehensively addresses necessary components including screening and surveillance; prevention training; assessment, treatment, and management of suicidal individuals.

Future research should focus on developing evidence-based universal prevention (e.g., peer-based, family-based, community-based, military/ecologically-based). The current prevention efforts must be evaluated for effectiveness. This research will need to establish evidence-based indicated interventions to prevent and manage suicide behavior across clinical care settings.

Alcohol and Other Drug Use

Drug (including prescription drugs) and alcohol abuse is a significant health problem in the military. Data obtained from the Armed Forces Health Surveillance Center reveal that the Army has the highest rate of acute alcohol diagnosis and substance abuse clinic treatment encounters within DoD. Additionally, almost 30 percent of the Army's suicide deaths from 2003-2009, and more than 45 percent of the non-fatal suicide behavior from 2005 to 2009, involved the use of drugs or alcohol. Increased prescription use among the military has led to heightened concern with overdoses, particularly from opiates. For many wounded warfighters, it is common to take multiple prescription medications for pain management, sleep, PTSD and other injuries, simultaneously.

DoD leverages the efforts of NIH; however, DoD also recognizes that there are still gaps in our understanding of substance abuse in the military. The DHP has funded a significant amount of substance abuse research that includes epidemiological studies as well as studies investigating prevention and treatment interventions. Further epidemiological research is needed to accurately characterize drug use (including alcohol, prescription drugs, tobacco, etc.) and misuse to include risk factors (e.g. co-occurring

disorders, domestic violence, danger to self and others), and to identify potential barriers to treatment seeking behavior. Substance abuse research is difficult to conduct within the military and is complicated by issues related to stigma, perception, and reality of negative consequences, culture, and policy.

CONCLUSION

Mr. Chairman, DoD continues to perform exceptional medical research for a population who deserves the finest medical care available. Our efforts demonstrate our obligation and dedication to improve the care of neurological and psychological injuries in the men and women of the Armed Forces. I am proud to represent the men and women who comprise the Military Health System research and development programs, and I thank them for their service.

Mr. Chairman, thank you for the opportunity to provide testimony today. I look forward to your questions.

[END]

Mr. KUCINICH. Thank you very much, Mr. Rauch.

We have a vote on. We are going to go for another 5 minutes. What I would like to do is, in deference to Mr. Kennedy, I am going to give him the first question here. After he concludes with his questions, we are going to go vote. Then we will come back here at 4 p.m., because five votes will take up about an hour.

So Mr. Kennedy, why don't you start.

Mr. KENNEDY. Thank you, Mr. Chairman.

First, I appreciate your contributions to this hearing enormously, and the testimony submitted and the points that you have made, and the questions that we will get into over the course of time when we come back I think will really bring some more illumination to all that and will be very useful.

But I want to take this opportunity in response to Dr. Rauch's point, first thank him for his service to our country in the military.

To hit one point home that I believe needs to get hit home hard, and that is, there is no difference between psychological and neurological. And if you want to know there is the highest suicide rates now against military, they are not supposed to have problems. But when we have a military that is talking about their problems in terms of 30 percent of the suicides are caused by alcohol, alcohol is caused by their combat wound. That 30 percent isn't alcohol, that 30 percent is a result of their combat wound.

And the last word about drug-seeking behaviors, no, self-medicating because they got a combat wound. Physical. We have a dual track, one, objective diagnostic tools for TBI as like a separate track from objective diagnostic tools from what you said, behavioral. It is not behavioral. It is physiological. Do you want to know why there is a stigma? Because the military refuses to talk about this as a combat wound, PTSD, physical changes in the brain as a result of prolonged exposure to cortisol.

We still have the leading medical experts coming up here and testifying, in spite of the report that was just released last week, which I would like to submit for the record, if it is all right with the chairman.

Mr. KUCINICH. Without objection.

Mr. KENNEDY. I think you were right, Dr. Rauch, about it being neurotrauma. But that doesn't apply to TBI, it applies to PTSD and TBI. I only can't hit this point home enough, because if we don't get to the stigma of mental illness, we are never going to get to the science. This notion that there is a dual track between the psychological versus the neurological, no way, wait a second. Let me just say, psychological is neurological. That is what we just learned on the board from the Director of the National Institutes of Mental Health. It is neurological. Stop calling it psychological. Stop calling it mental health and you will have less veterans feeling stigmatized by it, because we are the biggest stigmatizers, with that nomenclature.

When you have, and it is a fact, more veterans killing themselves in active service than are being killed in combat, there should be a wake-up as to what we are doing. The last commission report just released, no mention of the physiological impact of the trauma of war impacting suicide. All that we heard was psychological, behavioral, mental health. We re-stigmatized it.

That suicide commission was an utter disaster, in my opinion. Because all it ended up doing was laying on top to these veterans that somehow they have something that happens to them after war. No. This happened to them while they were serving, it is a combat wound. It is not alcoholic, it is not drug-seeking. It is a combat wound that ends up manifesting itself in these symptoms that then ultimately ends up as a suicide. And if we refer to it as alcohol-seeking behavior, drug-seeking behavior, something else, we do injustice to the fact that these veterans are stigmatized by their behavior because it is a result of their neurological changes that their service incurred on their brains.

And we can talk all day about science. But if we don't get this issue of stigma out on the table, we are never going to get anywhere, as far as I am concerned, Mr. Chairman. Thank you for allowing me the time.

Mr. KUCINICH. Thank you very much, Mr. Kennedy. We are going to recess until 4 p.m., at which time I will come back and I have questions for the panelists. Then we will go to the next panel after that.

I appreciate your patience and we will come back, and if the other members, Mr. Jones, Mr. Foster, if you are able to make it back, we would be very grateful.

Thank you, Mr. Kennedy. We are recessed until 4.

[Recess.]

Mr. KUCINICH. Thank you very much for your patience. We are going to resume the hearing.

Dr. Koroshetz had to leave due to a previously scheduled engagement, so we excused him from the panel of witnesses during the break.

We are going to resume with questions. Mr. Jones, we will go to you and then when all Members have had a chance to ask questions during the first round, I will ask mine.

Mr. JONES. Mr. Chairman, thank you for holding the hearing, and Mr. Kennedy, thank you for your leadership on this issue regarding mental health, but also the mental health of our soldiers and our families.

I want to very briefly, again, I talked about Camp LeJeune. A year ago, Dr. Kernan Manion, a psychiatrist, was released from his contract at Camp LeJeune. Because of that I asked for an investigation. And the IG is investigating his situation, but also from that situation, it has kind of expanded. Tom Bagosy was a sergeant, Marine sergeant that had been overseas twice. He was in the mental health counseling at Camp LeJeune, it was PTSD. Three months ago, he left the clinic at Camp LeJeune, and on McHugh Boulevard, he stopped his car and committed suicide at 11:30 a.m.

I want to ask you experts a little bit from the neurosciences to this point. Do you believe that the military mental health system could be helped if there was a national committee set up to evaluate military mental health, to make recommendations to the Department of Defense and to the Congress? The reason I bring this up is I have been very impressed with you. You are professionals, you are experts into an area that I am not.

But as a layman who has a military base in his district, and seeing the pain and the hurt that I have seen over the last few years, last story, and I would appreciate your answer about what can we do to strengthen military health. Can you imagine being able to speak at an elementary school at Camp LeJeune, Johnson Elementary School, National Reading Day, we are home because of the Easter break, I am reading Dr. Seuss to 12 kids sitting on the floor. And as I take questions at the end of, I say, you can ask me anything. The questions went, have you seen the President, do you have a wife, do you have a dog, those kinds of things. The last child, these are 6-year-old children, the last child, I said, this is my last question. He looked up at me and he said, my daddy's not dead yet. My daddy's not dead yet. Out of the mouth of a 6-year-old child.

Now I want to come back to what would be my only question of you. Are we at a point that the Congress needs to say to the President, whomever he is or maybe 1 day she, we need to put together a mental health commission of experts like yourself at the table to help our military develop a strong mental health program, whether we be at war or we be at peace? Does this have any validity?

Because what I am hearing, I know the hyperbaric oxygen treatment, we finally got it down at Camp LeJeune. They don't have the staff yet. But it seems like we are doing everything we can to deal with the mental health of our military, particularly those at war. But yet, it just seems like there are so many different aspects of it that somebody has to kind of bring it together and have it focus.

Does it make sense to have a commission to recommend to the military, to the Congress, to the President, of what we need to do to make the mental health program in our military stronger and better for the families?

Mr. RAUCH. Sir, I will start off. I think we need to work hard to leverage our existing collaborations right now that we have. They are very strong and they are very robust, with the VA and NIH. I have tried in my statement to focus on some examples. In my written statement, I have more examples.

But I think from my professional point of view, as a psychologist, I think the place to start is to work hard to leverage the existing relationships and collaborations that we have thus far with NIH and the VA on this issue of family studies, specific to the military.

Mr. KENNEDY. Walter, could I interject here?

Mr. JONES. Yes, sir.

Mr. KENNEDY. Do we have standard data points for TBI so that we can collaborate, so that a scientist from Rhode Island can talk to a scientist in his district on neuroscience? Because apparently in the second testimony that we heard, we don't, from Dr. Koroshetz's statement there is no standard TBI data input. So how can you talk about collaboration?

Mr. RAUCH. Sir, that is a good point. Remember that when we talk about traumatic brain injury, we are talking about a pretty broad spectrum. So that can range from mild, in concussion, to severe and penetrating and everything in between. There are a lot of differences in there. So it is a very, very broad spectrum.

I will turn it over to my colleagues, if they have a different view of the range of TBI.

Mr. KENNEDY. I think the whole purpose here, as Walter is saying, is that we are all in it together. Civilian research can benefit veteran research.

Mr. RAUCH. Absolutely.

Mr. KENNEDY. But if we don't have common data points and there are TBIs every night of the week from car accidents, and we can't collect anything that is useful to the veteran in terms of recovery, response, function, how can we be saying we are in it to win it for the vets? Tom, you have the blueprint at the NIH for a collaboration.

Dr. INSEL. Right. The blueprint has developed these programs for collaboration. As Walter Koroshetz mentioned, there is a real interest in what they are calling common data elements, which the neurology institute is putting out for all investigators to use for each of the disorders that they support. So that I think will be an important resource.

But if I may, could I go back to your original question? I think the perspective that you are describing is just very different from the personal experience I have had as a civilian representing a Government agency dealing with the leadership of the Pentagon. I have to say this, as clearly as I can, that the level of commitment to reducing suicide, to ensuring that resilience is supported, and to changing culture is greater amongst the leadership in the Pentagon than anything I have ever seen in the civilian sector.

These people really believe that this is their highest priority right now. They are very concerned about this issue. I have never seen that level of concern from anyone in the civilian sector, where in fact the suicide rate continues to take 34,000 lives a year.

So I think, I understand your wish to be helpful. But I do think that it underestimates what is already happening from an administration that really wants to make a difference here and is looking for answers quickly, and is trying out things quickly to try to bring this rate down and to try to make life better for soldiers in active duty.

Mr. JONES. Mr. Chairman, can I speak just very quick and I will finish?

Mr. KUCINICH. Go ahead.

Mr. JONES. I have great respect for the military. I didn't serve, but I have great respect. But this hyperbaric oxygen treatment that has been studied for years and years and years by the military, that is why they put a chamber down at Camp LeJeune, they are going to continue to study, I found out, talked to two people the other day, one was awarded the Medal of Honor in Vietnam for this country. He was so distraught about his grandson who had been severely injured, TBI, that he paid for him to go to the hyperbaric oxygen program at LSU.

I called him. He said, my son is just remarkably recovered. He can function now. He is not on drugs. So your point, I don't disagree with you. But this still, I am not saying it is the only treatment. You are the scientists. I am not. But I have talked to three different individuals, including a General Manny down at Florida, do you know him? Yes, you are smiling, so you do know who I am talking about. He was under the treatment at Walter Reed for months and months and months, saw no improvement. His wife

talked to the doctor at Walter Reed and she went to I think it was George Washington Med School. The doctor actually gave a prescription for him to be in the hyperbaric treatment program there.

This man has been in my office. He has been elected a State judge. He is functioning 110 percent. But if he would have stayed in the military, they would have kept him probably drugged for quite a bit of his life with no real improvement. So that is my concern. I don't fault anybody in the military. I think they do a magnificent job. But when you talk about working together, when you are talking about bringing people together, I just wonder if, as Patrick was saying, is there a formula that we can have for the military to know what is available without having people trying to duplicate other studies?

I just don't know, and that is the reason I wanted to sit here today. With that, I yield back.

Mr. KENNEDY. Well, Walter, you hit the nail, there isn't, to answer your question. Because there aren't common data points on TBI, which is the signature wound in the war, to help us instruct on whether those are injuries that affect and increase suicide rates. Just as of September 24th, I appreciate Tom standing up for his compatriots who are working hard, but Walter Reed Amy Hospital's chief of psychiatry, Colonel John Bradley, said shoddy training and coordination has left us a failure on taking on suicides in the military. From his own words.

So I appreciate your standing up for him. But when don't have the lead expert on mental health and suicides different psychological from neurological, after your testimony saying it is all neurological, you have a big problem here.

Mr. KUCINICH. I am going to ask the gentleman to hold some of that for the next round of questions. I have some questions, then we are going to have one more round, which the gentleman may lead off again.

Dr. Insel, I want to talk to you about the nature of stress. Stress produces chemicals which affect the brain, isn't that right?

Dr. INSEL. Correct.

Mr. KUCINICH. Can an abundance of stress in certain individuals bring about organic brain changes?

Dr. INSEL. We know that some of the stress hormones alter the way in which cells are born and cells die within the brain. So there is every reason to think that stress does have direct effects on the health of the brain. You will be able to hear a lot more about this from Dr. Akil, who is in the next panel, who is really one of the world's experts on this.

Mr. KUCINICH. Is there an area of the brain where frequent stress breaks down inhibition toward suicide?

Dr. INSEL. A lot of the research is focused on the effect of stress on an area called the hippocampus, which is certainly very important for higher cortical function, for memory, for the way in which memories get encoded in the brain. But the relationship of stress to brain anatomy or brain morphology and suicide remains now a very vague one. There are a lot of gaps in our understanding of how these things connect.

Mr. KUCINICH. I ask this question because, if it is not site-specific, then the work of someone like Karl Pribram, his holonomic

theory, comes into play. I am sure you are familiar with his theories.

Dr. INSEL. The places where stress is likely to have the greatest impact is where the receptors for hormones like cortisol, are found in the brain. And they are not everywhere. There are areas that are highly enriched. Those are places that we look, and in fact, those are the places where we see changes.

But again, there is a gap here between our understanding of the cellular effects of stress and our understanding of what causes suicide. It is a very complicated area when you try to predict, for instance, who is likely to take their own life. We know some of the factors from a population, but within an individual person, we are not very good yet at being able to have high levels of prediction.

Mr. KUCINICH. I heard you in response to an observation by my friend from North Carolina indicate work that is being done in the Department of Defense on matters relating to suicide. You did say that, correct?

Dr. INSEL. This is a joint project between NIMH and DOD.

Mr. KUCINICH. What is ironic about that, if I may, is that the stressor in this case is war. There is a "duh" factor about this. The latest book about President Obama and the Afghanistan war indicates the tension between the administration and the Pentagon, and the difficulty that the administration was having in having the Pentagon produce a plan to exit the war.

I think that my friend from North Carolina would agree, you can study the nature of suicide all you want. But if you have increased suicide that is coming from people who are in combat under horrendous conditions where there are all kinds of atrocities being committed, how smart do you have to be to figure this out?

So I appreciate that you are studying it. But it would be more productive, I think, if a group of scientists would come forward and have the opportunity to do some real tests on how stress breaks down people and how it puts them in that soft circumference of suicidal ideation, which then may lead to people acting and taking their own life. So you can't really speak to that, because that is not your area of decisionmaking.

But no matter how caring the people in the Pentagon are about the troops, as long as you are sending people into this mix-master of war, you are going to end up with suicides. Again, I don't think you have to be a neurophysiologist to understand this. I don't think you have to be a cognitive psychologist or cognitive neuroscientist to understand this. We put these young people into an impossible situation, they are killing themselves. I don't deserve a Ph.D. for that observation.

Now, is it true, Dr. Insel, that certain approaches to neuroscience necessarily depend on a mechanistic view of human beings?

Dr. INSEL. I am not sure I understand your question.

Mr. KUCINICH. Well, like Skinner, Skinnerian approach, stimulus-response. Behaviorism, if you induce certain stimuli, you get a certain effect. Are you a student of that particular type of neuroscience?

Dr. INSEL. That actually falls into a category of what would be called behavioral science. That really has to do with predicting behavior based on stimulus and response. One of the things that is

perhaps most conspicuous about that is that it leaves out the brain. So neuroscientists tend to think more about the mechanisms by which behavior gets regulated, and they tend to be a little more complicated than just the simple——

Mr. KUCINICH. Complicated. That is a good word. Tell me about it.

Dr. INSEL. The complications of how we predict behavior. Again, I need a little help here in terms of what it is you are looking for.

Mr. KUCINICH. When you talk about neuroscience, you could take an almost linear view. I am interested as compared with cognitive neuroscience, which encompasses the possibilities of quantum physics interfacing with neuroscience, where you actually create the potential of change that cannot necessarily be explained by the more linear progression of a more mechanical approach. Does that not register with you at all? If it doesn't, I will withdraw the question.

Dr. INSEL. Well, I am not sure I heard the question. But if the question is, does neuroscience provide a basis for approaching that complexity and trying to understand that complexity, I think the answer is yes. I think we have the tools now, many of which come from very different fields, such as higher math or from physics, from dealing with large amounts of information that we are able to actually begin to make sense of the complexity of how the brain works with models that become predictive.

We have a long way to go, but I would say that we have come a very long way from a simple Skinnerian model of stimulus and response.

Mr. KUCINICH. That is good to hear. Every component of the philosophy of science carries with it part of the headlong momentum of some of the early thinking within those disciplines. So I just wondered where a Skinnerian view fits in.

Dr. INSEL. In the testimony that I gave, Mr. Chairman, I used the term disruptive innovations. From my perspective, this last decade has been a series of truly disruptive innovations, as we have begun to understand, to go back to Congressman Kennedy's point, that the brain really is the gateway to understanding the mind. I don't believe that we had fully appreciated that in previous decades.

Mr. KUCINICH. I want to conclude by saying that, it may have been in, I don't think it was in your testimony, but maybe your colleague who just had to leave, spoke of the light shining on microbial membranes that opened up new channels. Is that what you are talking about?

Dr. INSEL. That is a technique that has been used to be able to study circuitry in the brain in a very precise way.

Mr. KUCINICH. I think you understand the comparison I am making, and that is that if you use light as a metaphor here, shining itself on certain membranes, opening up new channels, it is a metaphor for the possibilities of neuroscience to go into areas which would make the work that you are working out right now seem primitive in years to come, with all due respect. I am a fan of neuroscience's capabilities. So I appreciate your presence here.

Dr. INSEL. Thank you. If I may, just as a final comment about this, I think it needs to be said, we are in the middle of a revolu-

tion. In 20 to 30 years we will look back on this period to realize how little we knew. But the tools are there to transform the way we think about the brain. As someone said in the opening comments, this is really the last great frontier of science. For the first time, I think we have the discovery tools that we have needed to really explore and to colonize that frontier in a different way.

Mr. KUCINICH. Just one other question occurs to me. I don't know if you are able to answer this. But the phenomenon of fear, the emotion of fear. I have seen some studies that suggest that it originates in the limbic system, is that right?

Dr. INSEL. We use the term mediated.

Mr. KUCINICH. Mediated by the limbic system.

Dr. INSEL. Yes.

Mr. KUCINICH. And is that really, on an evolutionary standpoint, part of what some might call part of the reptilian brain, the flight or fight syndrome?

Dr. INSEL. Sir, those are models that we have kind of given up a few years ago.

Mr. KUCINICH. Well, I am talking about the archaeology of your discipline.

Dr. INSEL. The core, ancient part of the brain which feeds into those kinds of flight or fight impulses.

Mr. KUCINICH. Since you work with, since people in the neuroscience discipline work with the Department of Defense, is anyone doing any studies about the potential of transformation beyond fear, which often puts people into this fight or flight, which is a precursor for, inevitably, on a macrocosmic level, the precursor of war? Does anybody ever think about that?

Dr. INSEL. I am not sure that we are where you are on this idea. There is a tremendous amount of research right now on the fundamental neurobiology of fear and fear responses. And particularly what we call extinction, the ability to overcome fear.

But the relationship of that to war is a place where I think most neuroscientists haven't gone.

Mr. KUCINICH. Thank you.

Mr. Kennedy, second round.

Mr. KENNEDY. Thank you.

I think the most significant issue is how to do the research, so we make the most of what we know. It is not what we know, it is how much we don't know that we know. And that gets back to the common data points for TBI. But we can't do the data mining or find out what is working or what isn't, if there isn't common language and nomenclature.

You have a blueprint at NIMH. Does that blueprint include DOD and VA? And if not, why not? And to Dr. Kupersmith, do you have, along with the DOD and Terry, the ability to have a common program, computer program to input these data points or not?

Dr. INSEL. Just very quickly, we do have a blueprint, which is a consortium of I think 15 institutes and centers at NIH for some common projects. It is a fairly limited effort, it is identifying areas of common need and pushing ahead on a few of those. It does not involve DOD, VA or many of the other institutes at NIH, even. So it is truly a kind of homegrown project.

It has not in any way inhibited many of the institutes, my own included, NIMH, from these very large collaborations. As I said, the biggest project we are doing is the collaboration with DOD. And it has really become our signature project for 2010, and probably will be for the next few years. So the blueprint is not part of that. But it almost doesn't need to be. We have a lot going on just out of the institute itself.

Mr. KENNEDY. We don't have a program that allows for all this data to be put in so the scientists in one area of the country can find out what the scientists in the other areas of the country are doing, so we can work to greater effect, to everybody's advantage. We don't have that.

Dr. INSEL. We don't have a single data repository at this point for, other than for autism. I don't think that exists for any other area that our institute is working in.

Mr. KENNEDY. Would it be useful to everybody? I know you have these collaborations and it is helpful. But could we dedicate funding that would leverage what the institutes do by giving a little money to help bring them and their work together, to help and maximize each other in a coordinated way?

Dr. INSEL. We have done that in autism, and I think it has been transformative. We have an opportunity now for virtually every project to flow into the same data base called the National Data Base for Autism Research. That is a model that could be followed in a number of areas.

Mr. KENNEDY. That is terrific. Dr. Kupersmith.

Dr. KUPERSMITH. Our computers have not merged yet with DOD, but there is a tremendous amount of work on that. And that is a goal, certainly, of this administration. Our computer system evolved out of a clinical computer system sort of from the ground up with investigators creating software, merging into a large system. So that is clearly a goal of this administration, it is not a research topic, per se. Although research will benefit greatly from it. We are looking forward to being able to do that.

Mr. KENNEDY. Because if we don't know what we know, we are just doomed to repeat the science.

Dr. KUPERSMITH. Absolutely. And I think that quotes Albert Einstein, actually.

Mr. KENNEDY. Well, I am often confused for him in my intellectual passion for things. [Laughter.]

Dr. KUPERSMITH. There is very hard work, as many know, that is going on, very important.

Mr. KENNEDY. Thank you. And Terry, what would you say, Dr. Rauch, about the need to get DOD to help open what Tom has in his NIH and the VA, make it all, so everybody is helping to a common effort, both soldiers benefiting, and civilians benefiting from the soldier and vice versa.

Mr. RAUCH. You make a very good point, sir. We are working on it. We have a collaborative effort with VA, NIH, DOD, Department of Education. It is called the Common Data Elements project. And its purpose is to do exactly what you charged us to do, and that is to standardize terminology within TBI and the psych health portfolio. It is in development, it is in progress. But it has started.

I think I probably need to take this for the record and give you some more information. Your question really deserves a more detailed answer, and I would like to provide more detail on the Common Data Elements project for TBI and psych health.

Mr. KENNEDY. Super. Thank you. That is what the hearing is about: what can we do in Congress to help leverage what you are already doing and what the science shows us out there already.

Mr. KUCINICH. Congressman Kennedy, there is a person by the name of George Farre who was a physicist and is a philosopher. And he spoke to science as a structure-specific language, constructed for the representation of what there is. So semantics do count. Because they link through their expression to specific structures that help either to confirm pre-existing notions of a science or dis-confirm them.

So the point that you raised about the nomenclature is not a small matter. It is actually quite significant, not just for the subject of a particular type of behavior, but there are implications, broader social implications.

Mr. KENNEDY. I just want to repeat, Tom, what you said, to go fast, go alone, but to go far, you go together. But we need to go far together, but we need to go faster. If you can provide us some recommendations from your point of view as to what FDA can do, since they are integral in whatever comes up, your researchers, together if we can it right into the field for our soldier and our veteran. That would be very useful, if you can give us some ideas on regulatory science. Again, this is a process issue, as you have just said, Dr. Kupersmith. It doesn't involve the science, but the science can't be maximized unless you get the process right.

So if you could provide us some input on that, as you have already in your testimony, it helps us make a better case politically, that if we just put some dollars here, we leverage a whole bunch. If we work as a team, we get further. And your blueprint is a perfect, how do we institutionalize that more, get the common data sets and standardized terminology together. So that would be useful.

Mr. KUCINICH. Thank you, Congressman Kennedy. I just have a couple brief questions and we will go to our next panel. One of you gentleman brought up nutrition, was it you, Mr. Rauch? In what context did you bring that up?

Mr. RAUCH. I brought that up in the context of nutritional interventions in the whole psych health/TBI/PTSD portfolio, to include looking at nutriceuticals. That is an area in which we have a number of projects that we are funding.

Mr. KUCINICH. John Robbins, the author, has written extensively about the impact, adverse impact on human health of certain types of foods. There has been plenty of research about the adverse impact on physical and mental states in consuming large amounts of sugar. We know it is true of large amounts of salt. There have been studies done on prison populations whose diets have changed and it has, a change in diet produced changes in their emotional states, made them actually less aggressive.

I think that the potential for neuroscience making a great contribution is there, there is no question about it. It is really urgent

that we use whatever means we have available to help fulfill its potential.

So I want to thank the members of the first panel for your commitment in your respective disciplines, for your thoughtful testimony and question answering that you provided. This is an area which Congressman Kennedy, I think that in the next Congress, we ought to think about doing some followup hearings. We ought to think about——

Mr. KENNEDY. I will be sitting back there, Mr. Chairman, looking up at you.

Mr. KUCINICH. You will always be welcomed. I think what you have done is you have, through your becoming involved in this, we have become aware there are examples of research collaboration between and among Federal agencies. What you have done is to remind the people in the community that it is important to collaborate with each other. Whether it is done on ad hoc process or on a regular basis, I think that it is and can be productive because of the synergy that always comes from interdisciplinary thinking.

So I would urge that an approach of interdisciplinary thinking to continue through encouraging all the parties to this to keep talking, if they are, and to start talking together if they are not. I think it is a good idea to work collaboratively with your friends in Congress who will advocate on your behalf in the appropriate venues.

Thank you for being here, and good luck with your work, and we are going to call the second panel.

While the second panel is getting into place, I want to thank them and the members of the audience for your patience. Because of the congressional voting schedule, we have had kind of a prolonged hearing here. Your willingness to come here to offer testimony and answer questions is much appreciated.

I am going to introduce our second panel. Dr. Huda Akil, Ph.D., is the Gardner Quarton distinguished University professor of neuroscience and psychiatry and the co-director of the molecular and behavioral neuroscience institute at the University of Michigan. Dr. Akil has made seminal contributions to the understanding of brain biology, of emotions, including pain, anxiety, depression and substance abuse. Dr. Akil has received several awards for her research and is past president of the Society for Neuroscience. Thank you, Dr. Akil, for your presence.

William Z. Potter, M.D., and Ph.D., spent 25 years at the National Institutes of Health focused on translational neuroscience. While at the NIH, Dr. Potter developed a wide reputation as an expert in psychopharmacological sciences and championed the development of novel treatments for CNS disorders. In 2004, Dr. Potter joined Merck Research Labs as VP of Clinical Neuroscience and assumed the newly created position of VP of Transactional Neuroscience in 2006, a position from which he retired in January of this year. Thank you very much, Doctor.

Timothy Coetzee, Ph.D., is the executive director of Fast Forward, LLC, the National Multiple Sclerosis Society's drug discovery and development affiliate. In this capacity, Dr. Coetzee is responsible for the Society's strategic funding of early stage biotechnology and pharmaceutical companies engaged in the discovery and devel-

opment of new treatments and diagnostic tools for multiple sclerosis. Thank you, sir.

Kevin Kit Parker, Ph.D., is the Thomas D. Cabot associate professor of applied sciences and associate professor of biomedical engineering at the School of Engineering and Applied Sciences at Harvard. Professor Parker is the director of the Disease Biophysics Group and a member of the Systems Biology Department at Harvard Medical School, Harvard Stem Cell Institute and the Harvard-MIT Health Sciences and Technology program.

He is also a major in the Rhode Island Army National Guard and has completed two combat tours in Afghanistan with the 82nd Airborne and the 10th Mountain Division. Thank you for being here, sir.

John H. Morrison, Ph.D., is the dean of basic sciences and the Graduate School of Biological Sciences at Mount Sinai School of Medicine. Before becoming Dean, he served as the Chair of neuroscience. Dr. Morrison is also professor of neuroscience and the Willard T.C. Johnson professor of geriatrics and adult development in neurobiology of aging. Thank you.

This is a distinguished panel, as was the last one. It is our policy in this Committee on Government Oversight and Reform to swear in all witnesses before they testify. I would ask that the witnesses stand, raise your right hands.

[Witnesses sworn.]

Mr. KUCINICH. Thank you. Let the record reflect that each of the witnesses has answered in the affirmative.

As with the members of the first panel, I would ask you to try to keep your remarks to 5 minutes. And as with the members of the first panel, I let them go on, because they had some things to say that were very important.

Mr. KENNEDY. In that regard, Mr. Chairman, I just want to thank everybody who showed up today. All of you represent different organizations, groups and have been very useful in helping put this hearing together. I want to thank Zach Lynch from the Neurotechnology Organization who has been very useful in helping put together some very helpful statistics and points for us in the hearing, and just say, we wish we could get everybody up here. Because everybody in this audience, from looking out on this audience, I am familiar with in this field. But just appreciate that we understand and have incorporated a lot of your recommendations and suggestions into the hearing. And thank everybody for being here today.

Mr. KUCINICH. Thank you.

Dr. Akil, you may begin. Thank you.

STATEMENTS OF HUDA AKIL, PH.D., CO-DIRECTOR AND RESEARCH PROFESSOR, THE MOLECULAR & BEHAVIORAL NEUROSCIENCE INSTITUTE, UNIVERSITY OF MICHIGAN; WILLIAM Z. POTTER, M.D., PH.D., FORMER VICE PRESIDENT OF TRANSACTIONAL NEUROSCIENCE, MERCK RESEARCH LABORATORIES; TIM COETZEE, PH.D., EXECUTIVE DIRECTOR, FAST FORWARD, LLC; KEVIN KIT PARKER, PH.D., ASSOCIATE PROFESSOR OF APPLIED SCIENCE AND BIOMEDICAL ENGINEERING, HARVARD UNIVERSITY; AND JOHN MORRISON, PH.D., DEAN, BASIC SCIENCES AND THE GRADUATE SCHOOL OF BIOLOGICAL SCIENCES, MOUNT SINAI MEDICAL CENTER

STATEMENT OF HUDA AKIL, PH.D.

Ms. AKIL. Mr. Chairman, Mr. Kennedy, members of the committee, thank you for this opportunity to testify here today.

I wanted to mention that beyond my service as the past president of the Society for Neuroscience, I am a member of the Council of the Institute of Medicine and its forum on neuroscience. I am also a co-chair of the steering committee of the Biomarkers Consortium at the Foundation for NIH.

I currently hold funding from the NIH, the Office of Naval Research and the Pritzker Foundation to conduct work on the biology of stress, emotions, addiction and mood disorder. As an aside, given the discussion in the earlier period, we are studying in the Consortium the brains of people who were depressed and committed suicide versus the brains of people who did not and whether they were being treated or not. We are beginning to get some insights to your question about where in the brain the changes might happen. That is not the focus of my testimony today, but I am happy to answer questions about it.

So as we have heard, the global burden of brain disease is staggering. The challenge of understanding, preventing and curing brain disorders is still very much before us. Today, what I wanted to do is outline what I believe to be the central grand challenge of neuroscience, one that is relevant to all the brain disorders that we have been talking about. I would like to suggest a couple of strategies for meeting it.

Our brain contains 100 billion cells that communicate via 500 trillion connections or synapses. The point of all this communication is to orchestrate brain activity. Each brain cell is a breathtaking piece of biological machinery. But a single cell can never perceive beauty or feel sadness or solve a mathematical problem. Through the magic of integration, completely new capabilities emerge. When networks of brain cells come together to form brain circuits, each of which perform specific functions, such as vision, hunger, cognition, emotions.

I call this neural choreography. By the time a brain disorder is evident, it has affected not a single group of cells, but the entire circuit. It is the disruption of the whole network that leads to the symptoms of the illnesses that we are concerned about. The problem is not that a ballerina has stumbled, but that the choreography of the whole ensemble has fallen apart.

So when we are thinking about the impact of brain injury on movement, the exaggerated response to a threat signal in a soldier with PTSD, the drug compulsion in an addict, the confusion about reality in a psychotic patient, we have to think about disrupted brain circuits, neural choreography gone awry.

And our grand challenge is to understand the workings of a brain circuit and learn how it controls itself. As Dr. Insel has indicated, we know the elements of many of these circuits. But we need to watch them perform in real life, in real time, and discover how their choreography fails and how that causes disease.

The idea that brain disorders are the result of faulty brain circuits also explains why it has been so hard to uncover genetic causes of some disorders that we know to be very heritable, like bipolar illness. It is because the symptoms that clinicians diagnose are manifestations of a disrupted brain circuit and there are countless ways to screw that up. So different families can suffer from completely different genetic problems and still share the same medical diagnosis. It is like any given dancer in the troop can fail and disrupt the whole dance.

But the choreography idea also means that there are multiple ways to repair the problem. We don't need to devise a new treatment for each family. We need to learn how to retune the circuits, the networks.

So how do we take on the neural choreography challenge? My inspiration for tackling it comes from the brain itself, the creation of well-orchestrated networks of scientists who work together to achieve what can never be achieved separately. This effort needs to be grounded in some hard-earned realities. In the words of President Kennedy, we need to be idealists without illusions. Understanding the brain and mind is hard. And we need help, not only from each other, but from our colleagues in math, physics, chemistry and engineering. We also need to engage our friends in the social sciences, since our brains are constantly being remodeled by our social environment.

But the knowledge that can emerge from such networks can be transformative, and the discoveries unimaginable. I have suggested in my written testimony three types of integration: horizontal integration, where a large number of investigators with the same general expertise focus on a given slice of a problem, for example, validating biomarkers over disrupted brain circuits, say in PTSD. Vertical integration among different scientists who are focusing on a scientific question or disorder and trying to solve it from molecule to mind and back. Neural choreography is right in the middle of that path.

And finally, two-dimensional integration that represents special large-scale projects that combine vertical and horizontal efforts. The goal would be to advance our fundamental knowledge of neural circuitry and relate the discoveries not to one disease but to several disorders.

But whatever the model, rather than being entirely investigator-driven or agency-driven, I believe that this process needs to arise from a partnership between the scientific community and the Federal agencies, to get buy-in and to define the specific approaches that would be most fruitful.

So in summary, understanding the brain and healing it when it is sick may well be the most difficult challenge that humanity has ever undertaken. We need to give this amazing organ its due by bringing together every tool we have at our disposal and working together to probe its mysteries. Thank you.

[The prepared statement of Ms. Akil follows:]

Testimony

Of

Dr. Huda Akil, PhD

Gardner Quarton Distinguished University Professor
Of Neuroscience & Psychiatry
Co-Director
The Molecular and Behavioral Neuroscience Institute
University of Michigan

Before the

Committee on Oversight and Government Reform
Domestic Policy Subcommittee
United States House of Representatives

September 29, 2010

Mr. Chairman, Ranking Member Jordan, and distinguished Members of the Committee, thank you for inviting me to testify here today. Understanding and treating brain disorders is a topic I care deeply about, and pursue both in my own scientific research and in my public service. I am the Gardner Quarton Distinguished Professor of Neuroscience and Psychiatry at the University of Michigan and the co-Director of its Molecular and Behavioral Neuroscience Institute. I have served as President of the Society for Neuroscience (SfN) and currently serve on the Council of the Institute of Medicine of the National Academy of Sciences, and on the IOM Forum on Neuroscience and Nervous Systems Disorders. I also co-chair the Neuroscience Steering Committee of the Biomarkers Consortium at the Foundation for NIH.

I have had the good fortune of receiving continuous funding for my research from the National Institute of Health (NIH). I have held NSF grants and currently have a grant from the Office of Naval Research (ONR) focused on the biology of stress and PTSD. Our research group is part of the Pritzker Consortium, a large collaborative effort that aims to understand psychiatric diseases, supported by the Pritzker Philanthropic Fund. I enumerate these sources of funding not only to express my gratitude for the support, but to indicate my familiarity with funding mechanisms from federal and private sources.

Thanks to federal funding, our knowledge of neuroscience has advanced at a remarkable pace. We now know an immense amount about the brain relative to even a decade ago. This knowledge has fueled remarkable advances in the treatment of many brain diseases. Yet the challenge of understanding, predicting, preventing, treating or curing brain disorders is still largely before us. The burden of these brain disorders is staggering, with

neurological disorders affecting up to a billion people worldwide[1,4] and psychiatric and addictive disorders impacting comparable numbers.[2] Moreover, the disability burden of brain disease is huge, especially in low and middle-income countries where 80% of the mentally ill people live.[2] But beyond the health and economic costs[3] is the nature of these diseases, which are devastating to patients and their families, sometimes changing the affected person's very identity. Today, I outline what I believe to be the "Grand Challenge of Neuroscience" and suggest strategies for meeting it in order to advance our understanding of these disorders.

A- The Grand Challenge: Understanding "Neural Choreography"

Why "Neural Choreography"?
By the time a brain disorder is evident, it has typically affected not a single, uniform group of brain cells but a brain circuit, and it is the disruption of that circuit that leads to the symptoms of the illness. By analogy to a ballet performance, the problem may not be that a ballerina has stumbled, but that the choreography of the whole ensemble has fallen apart. Such a problem may be more subtle and harder to pinpoint, but it is no less disruptive. *I am using "neural choreography" to describe both our current scientific challenge and our path forward in attacking the problem of brain disorders.*

The brain contains approximately one hundred billion brain cells that communicate with each other via specialized connections or synapses. A typical adult brain has 100-500 trillion synapses.[5,6] *The point of all this communication is to orchestrate brain activity.* Each brain cell or neuron is a breathtaking piece of biological machinery that performs beautifully--genetically, biochemically and electrically. But no matter how accomplished, a single neuron can never perceive beauty, feel sadness or solve a mathematical problem. Through the magic of integration, completely new capabilities emerge when networks of neurons work together. Thus, ensembles of brain cells, sometimes quite far flung, form an integrated "neural circuit" and the activity of the network as a whole supports specific brain functions such as vision, hearing, hunger, sleep, learning or emotions.

We have made great progress in identifying the participants in these networks for some brain functions such as vision—the location of the relevant neurons, the chemicals they use to communicate with each other, the way they integrate information leading to the perception of a color, a form or a movement. For other brain functions, we may still be missing some important actors—for example the brain circuit that mediates mania in a person suffering from Bipolar Disorder is not nearly as well identified as that which mediates Parkinson's Disease.

---

[1] Neurological disorders affect millions globally: WHO report (Feb. 2007)
[2] W.H.O. Report: Mental health and development: targeting people with mental health conditions as a vulnerable group (released September 2010)
[3] http://www.bocyf.org/benefit_cost_workshop_highlights.pdf
[4] http://www.sfn org/index.aspx?pagename=brainfacts
[5] http://www.sfn.org/index.aspx?pagename=core_concepts
[6] Drachman D (2005). "Do we have brain to spare?". *Neurology* **64** (12): 2004–5. doi:10.1212/01.WNL.0000166914.38327.BB. PMID 15985565.

But aside from identifying the participants, *our main challenge is to understand the workings of the circuit as a whole, its dynamics and how it controls itself. We need to watch these circuits as they perform in real time, and watch how their choreography fails in each disease.* This is important because these dynamic features are the very basis of what goes right, and wrong, in our brain. Whether we are talking about a smooth walking gait that is disrupted in Parkinson's disease, the capacity to deal with a threat signal that is damaged in a soldier with PTSD, the ability to resist a drug that is lost in an addict, or the discrimination between reality and fantasy that is erratic in a psychotic patient, we have to think about disrupted brain circuits- neural choreography gone awry.

Neural Choreography and the Search for Causes of Brain Disorders

The view that the majority of brain disorders result from disrupted neural circuits has profound implications for the way we search for the causes of brain disorders. Even for illnesses such as Bipolar Disorder or Autism that are clearly familial and highly heritable, the quest for clear genetic causes has been more difficult than anticipated. Why? Because what we diagnose is the result of a disrupted brain circuit and there are countless ways to bring about this disruption--any given dancer in the troupe can fail in the fine-tuning of a dance movement and disrupt the overall choreography.

Indeed, this is the basis of an opinion piece that we have recently published in Science entitled: *"The Future of Psychiatric Research: Genomes and Neural Circuits"*.[7] While this article was focused on psychiatric diseases, the same logic can be applied broadly to other complex brain disorders including neurological and addictive disorders. The rationale is based on the view that *different families can suffer from completely different genetic problems and still share the same medical diagnosis.* This is because the disruptions caused by these genetic problems converge on a common brain circuit, which in turn results in shared symptoms and a shared diagnosis. Thus, beyond genetic "complexity" which refers to the existence of multiple genes each of which contributes to vulnerability to the illness, we need to consider the possibility of "heterogeneity" where non-overlapping genetic causes can lead to a common disease. This recalls the opening sentence of Leo Tolstoy's Anna Karenina: *"Happy families are all alike; every unhappy family is unhappy in its own way".*

Beyond the heterogeneity in genetic causes, we need to recall that the brain is in the business of remodeling itself based on *experience.* This is not a minor feature of brain function but rather represents the essence of how the brain operates in order to cope with a complicated and unpredictable world. *Therefore, environment matters and interacts closely with genetics in either increasing or buffering the risk for disease.* This is particularly true in early childhood when our brains are most adaptable, but is certainly true during adolescence when the brain is undergoing dramatic remodeling, and continues into adulthood and old age. Thus, two people could carry the same genetic load but have

[7] Akil H, Brenner S, Kandel E, Kendler KS, King MC, Scolnick E, Watson JD, Zoghbi HY. The future of psychiatric research: genomes and neural circuits. ***Science.*** 2010 Mar 26;327(5973):1580-1. PMID: 2033905

a very different outcome in terms of disease due to their environment. *Brain is where nature and nurture most clearly meet.* This is both a complication and a source of hope.

The central role of brain circuits, the heterogeneous nature of the genetics and the role of the environment in brain diseases might also speak to the challenges of developing treatments, since patients can share a common diagnosis but have a differing underlying cause of their illness. But the circuit idea means that we do not need a different medication for each family. There can be multiple ways to repair the problem by adjusting the choreography—we can help other dancers alter their movement or tempo and produce a new smooth balance.

B. Meeting the Challenge: Choreographing Research Teams of the Future

General Considerations: President John F. Kennedy said: "*I'm an idealist without illusions*". Similarly, we need to strive to conquer our grand challenge while being grounded in some hard earned realities:

1) Understanding the brain and mind, and using this knowledge to cure brain disease may well be *the hardest scientific problem that humans have attempted.*
2) *We need to rely on every conceivable approach to probe the brain—no holds barred.* We need help— not only from each other, but from chemists, physicists, mathematicians and engineers. Moreover, since we are embedded in a social environment that literally shapes and reshapes our brain, we need to seriously engage our colleagues across the social sciences in this quest.
3) *Nevertheless, partial understanding can lead to new treatments.* We have, in fact, made immense progress, which indicates that deeper understanding of the brain is doable. And this has resulted in better treatments, which shows that we do not need to fully solve a problem before we make an impact on people's lives.
4) *Knowledge in neuroscience is a two-way street-* Studying the normal brain is essential for understanding what goes wrong with it. Conversely, studying the diseased brain reveals a great deal about the normal workings of healthy brains.
5) *Fundamental principles of brain function and dysfunction are shared.* While the circuit involved in each function is unique, and while the molecular culprits for each disease vary, dramatic advances in one area clearly advance the entire field.

A Proposed Approach:

The inspiration for tackling the complexity of the brain comes from the brain itself- *the creation of well-orchestrated networks of scientists who work together to achieve what can never be achieved separately.* Just as new capabilities emerge in the brain when networks of neurons work together in a well-oiled manner, so do dramatically different insights emerge if we bring together researchers who have differing specialties and vantage points. The process can be transformative and the discoveries unimaginable.

I hasten to add that I am not recommending, by any stretch, the dissolution of the classical small team of scientists that makes up the majority of current neurobiological research. This model has served neuroscience extremely well, specifically because we have so much to discover. The diversity of minds, strategies, tools and interpretations that come from having a large number of independent scientists thinking originally about the myriad facets of brain function is critical for our continued success. There also exists another layer of science where research groups are larger, or where projects rely on collaborations between multiple small labs, using funding mechanisms such as NIH Program Project Grants or Center Grants, and those should be preserved as well.

What I am suggesting is: a) supporting new mechanisms for greater integration within the NIH, between funding agencies, and between government and industry; b) defining integration in more than one way; and c) creating a partnership between the funders and the scientists to identify the questions and strategies that might be most fruitful.

Horizontal Integration: With this approach, one gains power by bringing together a significant number of investigators with the same general class of expertise focused on solving a given aspect of a problem, for example the validation of biomarkers for a brain disease. A highly successful example of such an effort is the Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private collaboration which aims to discover biomarkers for AD. Results from ADNI promise to transform the diagnosis and development of drugs for AD and other types of age-related cognitive disorders.

Vertical Integration: involves focusing on a core scientific question by bringing together expertise from within and outside of neuroscience. The initial question can be basic or clinical in nature, but the vertical integration should erase these boundaries, allowing the team to follow the most promising leads and move bi-directionally from the most fundamental to the most clinical and back. For example, in our search for genes of psychiatric diseases, we need the expertise of clinicians, geneticists, neuroscientists, and computational biologists. But the identification of one or more gene that contribute to the vulnerability to, say, bipolar disorder is only the start of the journey. "Reverse translation" work is needed to understand the basic functions of that gene and its role in particular brain circuits both in animal models and in humans. Such work can lead to the validation of biomarkers for the illness and the identification of new targets for drug development that can be pursued in collaboration with industry. Ongoing work in the Pritzker Neuropsychiatric Disorders Research Consortium[8] exemplifies this model. A similar project focusing on PTSD would be highly feasible.

Two Dimensional Integration: represents special large-scale projects that combine both vertical and horizontal integration. The goal of such an effort is to *address a fundamental question in neuroscience and study its implications across a range of brain disorders*. For example, we can ask how a normal brain circuit achieves optimal control of its functioning, and what can cause brain circuits to become unstable. This is relevant to many disorders such as epilepsy, bipolar illness and chronic pain. By focusing on a

[8] http://www.pritzkerneuropsych.org/about/overview.htm

shared central problem—unstable circuit dynamics, regardless of disorder, we can use the convergence of information to extract the central features of a stable versus unstable brain circuit- the well choreographed versus the badly choreographed networks.

This approach has the potential to move from molecule to mind and back to molecule. Discoveries may well inform many other disorders than those initially investigated. This understanding can help us devise ways to reset the balance of that circuit either by directly replacing the defect, or more likely by retuning it elsewhere. And we can set the stage for partnerships with industry that lead to new treatment modalities, be they drugs or other types of interventions that help overcome the disease.

Creating a partnership between the funders and the scientists These proposed teams of the future may require integration not only across agencies, but also across laboratories, universities and disciplines. I believe neuroscientists can be comfortable with such efforts, as the discipline is intrinsically highly multidisciplinary—we exemplify E.O Wilson's view: "Complexity is what interests scientists in the end, not simplicity".[9]

But whatever the model, it is critical that the scientific community have a strong voice in helping define the parameters of the scientific questions and the strategies for attacking them. Researchers in the field typically perceive the funding process as binary-- either *investigator-driven research* (e.g. RO-1 or Program Project Grants), whereby scientists generate ideas for evaluation through peer review, or *agency-generated programs,* whereby agencies issue a program announcement and investigators attempt to adapt their research to the parameters of the program in order to compete for funding. It is the case that many agencies seek extensive expert input as they define the programs that they plan to announce. But this is not a highly visible aspect of the process, and many investigators are wary of what they perceive to be agency-driven "big science". *If we were to undertake large scale, inter-disciplinary efforts in neuroscience that may involve multiple funding agencies, it would be very important to devise a highly visible, iterative process that requires collaboration between the funding agencies and the scientific community in defining the scope and the nature of these projects.* Any program announcement would be informed by this input but kept sufficiently flexible to allow for ideas that had not surfaced in previous discussions. In many ways, this would be a hybrid between the investigator-driven and the agency driven mechanisms. Such a partnership between the funding agencies and the scientific community is essential for getting broad buy-in from the scientific community, identifying the areas that are most ripe for in depth analysis, and educating the peer review system in evaluating such projects.

C. Conclusions

Understanding the brain and healing it when it is sick may well be the most difficult challenge that humanity has ever undertaken. We need to give this amazing organ its due, by bringing together every tool we have at our disposal and finding new ways of working together to probe its mysteries.

---

[9] E.O. Wilson, "Consilience· The Unity of Knowledge", 1998, Knopf.

Mr. KUCINICH. Thank you.
Dr. Potter.

STATEMENT OF WILLIAM Z. POTTER, PH.D.

Dr. POTTER. Mr. Chairman, Mr. Kennedy and members of the committee, I am speaking from the perspective of a retired officer in the Public Health Service and a practicing psychiatrist. I served in intramural programs of the National Institute of Mental Health for 25 years, and I have just retired from the pharmaceutical industry, where for the last 15 years, I worked with a couple of big companies, Eli Lilly and Merck, which had big investments in CNS drugs.

Despite the sensational advances in neuroscience during this period, and the explosion of sophisticated technologies you have been hearing about, we have not delivered truly novel drugs for diseases of the brain. Arguably, the current generation of psychiatric medications for treating schizophrenia, depression and severe anxiety are no more effective than the first generation of medications discovered over 50 years ago, and those by accident.

The assumption back in the 1980's at all levels of Government and industry was that scientific explosion would rapidly lead to more scientific treatments. But that was overly optimistic. If anything, the opposite has been the case. It has become much more difficult to develop the novel targets that were identified, and to bring a single new entity to market now costs on average $1.8 billion, which is actually a pretty conservative estimate of the real costs.

The new drugs, and this is for all drugs, new drugs for brain diseases emerge at even a lower rate and prove more expensive to develop and carry extremely high risks.

So what went wrong with our predictions from the 1980's? And as Dr. Insel has pointed out, we have a new revolution to incorporate into our future thinking.

So what went wrong was the assumptions were too simple, as Dr. Akil has currently addressed. So the complexity at both the genetic and physiological level was much greater than we ever anticipated, and we did not have the maps or navigational tools to go through all this data and pick out the right targets.

So what we are up against is this wall of what we call target validation, what are the right things to make drugs for. Instead of a few drug targets, we have hundreds now that we need to sort through. And it requires us to sort through a single one that we think might be valid, which takes us over 13 to 14 years and get it through regulatory review and to the market, if you are in the business of the industry. For the central nervous system area, at best, 1 in 20 of the things we that into this expensive and long development actually deliver.

So obviously, with that sort of numbers, it is not possible for the pharmaceutical industry to survive by investing in the CNS field, without a huge paradigm shift. Given long development times under the current laws, most drugs will have 10 years or less of patent protection by the time you have been through this. And ironically, the "me-too" drugs, which are easier to develop, are actually the ones that enjoy the longer patent protection. So the incen-

tive structure actually rewards coming up with "me-too" drugs, and says, don't waste your money on coming up with novel, better drugs. But this is basically why many companies have reduced their investment.

So in one area we have an exception, fortunately, and that is around the field of Alzheimer's. And there, both the NIH, clinical scientists, patient advocacy groups, philanthropies, FDA and industry joined together under this remarkable effort sponsored by the National Institute of Aging called the Alzheimer's Disease Neuroimaging Initiative.

In keeping with some of what Mr. Kennedy has already discussed, the findings become available on computer, available all in the public domain, as soon as the data is gathered and processed. This ADNI model has taken hold worldwide and is currently trying to be implemented in the European Union, Japan, Australia and Korea. Fundamentally, their governments have said, this area of translational medicine and the tools and the data sharing necessary to support it are national priorities.

We use this term translational medicine to cover all the science and technology to help us translate the basic science that Dr. Akil was talking about into something that might be useful for patients. But to realize the promise of these scientific advances, we have to invest a great deal more in the tools of translational medicine, an area which sort of falls in the middle and gets less support than the basic science at one end, or the large clinical trials of the drug companies at others.

So the right balance of resources across the domains of basic research, translational medicine, clinical trials, has yet to be achieved. We need to expand this open source model, which Mr. Kennedy has already been referring to. So the first major recommendation of what can we do better is get more open sharing of all relevant clinical data on the characterization of the disease state and drug response. Obviously you need to protect individual privacy.

And the second big push would be to put the research tools and compounds held by both commercial entities and universities and private and funded investigators into the public domain, into what we call pre-competitive space, get that out there as quickly as possible. And to make that possible, we probably do need innovative approaches to the intellectual property issues which currently impede this sharing of technology and data.

I will stop there, but I can go into much greater detail of how this might work.

[The prepared statement of Dr. Potter follows:]

Testimony
Of

William Z Potter, MD, PhD

Captain (retired), US Public Health Service
VP of Translational Neuroscience (retired), Merck Research Laboratories

Before the

Committee on Oversight and Government Reform
Domestic Policy Subcommittee
United States House of Representatives

September 29, 2010

Mr. Chairman, Ranking Member Jordan and Members of the Committee I am speaking from the perspective of a retired officer and practicing psychiatrist/researcher in the Public Health Service where I served in the Intramural Programs of the National Institutes of Health for 25 years and a just retired executive from the pharmaceutical industry. For the past 15 years I worked on discovering and developing drugs in two companies, Eli Lilly and Merck, which have had large investments in finding new drugs for brain diseases.

Despite the sensational advances in neuroscience during this period and explosion of sophisticated technologies within academia and industry we have not delivered truly novel drugs for diseases of the brain. All of the currently marketed major classes of drugs for brain disorders were discovered before the era of molecular science. While the current drugs for treating severe mental illnesses such as schizophrenia and depression are indispensable -- it would be difficult if not impossible to effectively treat these conditions without them -- they are unfortunately not as effective as we would desire. Fully 2/3 of patients with depression or schizophrenia never achieve full remission and another 1/3 do not respond much at all. Arguably the current generation of psychiatric medicines for treating schizophrenia, depression and severe anxiety are no more effective then the first generation of medicines discovered over 50 years ago -- and most of these by accident!

The assumption at all levels of government and industry that the scientific explosion beginning in the late 1980's would rapidly lead to more effective treatments was overly optimistic. If anything, the opposite has been the case. It now takes longer and costs several times more to deliver truly innovative drugs to the market than two decades ago as the bar has been raised.

Taking into account drugs for all diseases, only a half dozen first in class molecules are delivered per year at four times the cost. To bring a single new entity to market now costs, on average, of 1.8 billion dollars, a conservative estimate. The detailed assumptions and figures have been recently presented in a major journal with no one questioning their validity.[1] New drugs for brain diseases emerge at a much lower rate, prove more expensive to develop and carry one of the highest risks of any class in terms of negotiating the minefield of discovery and development.

What went wrong? It was assumed that understanding brain biochemistry and processes through modern science would increase the rate of matching specific abnormalities to specific drugs. After all, even with the science of the 60's, scientists had figured out that one could help Parkinsonism by replacing the

neurotransmitter dopamine. Coupling modern techniques with genetics. It seemed a sure bet to find many more such relationships between specific defects and diseases.

As my distinguished academic colleagues have or will testify in detail, most brain diseases have turned out to be much more complicated than anticipated. This is true both at the level of genetics and physiological processes. Instead of a few possible drug targets based on the model of one defect, one disease, we now consider hundreds without any established map or navigational tool. Animal models for brain diseases (with the exception of symptomatic epilepsy) have poor predictive qualities for human brain diseases. This is not surprising given species differences. Moreover, animals do not spontaneously show analogous conditions for such disorders as schizophrenia.

Investigators in the public and private sectors are therefore up against the wall of what we call "target validation"– put in other words, a valid target is one through which a specific drug produces benefit. Literally hundreds of potential therapeutic drug targets have been identified for our major psychiatric and neurologic diseases but only a handful of them validated. Almost all of the hundreds of targets identified through modern molecular science still require substantial resources and time to validate. Even without counting the years of basic science to suggest that a drug target is worth trying to validate in the clinic it requires an average of 13.5 years (2007 data) to discover and develop a compound and take it through regulatory review.[1] Moreover, only 1of 20 of central nervous system (CNS) drug targets selected for development will prove effective for some condition and reach the market.

There is no way, therefore, that the pharmaceutical industry can profitably deliver innovative and breakthrough medications for brain diseases to society without a paradigm shift. Levels of investment and time become even more prohibitive for developing drugs that might prevent or slow the progression of diseases, the Holy Grail of patients and clinical neuroscience. Given long development times and current laws many if not most drugs will have only 10 years or less of patent protection in the U.S. This is because in the U.S. the patent clock begins ticking when a patent is filed -- many years before the new medicine makes it to the market and importantly to the patient. . Since "me too" drugs are easier and more quickly developed, they enjoy longer patent protection

---

[1] Paul SM, Mytelka DS, Dunwiddle CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery 2010 Mar 9 (3): 203-214

and have been a great economic driver. But they do not provide what patients are waiting for. Sadly, the period of patent exclusivity is not long enough to recoup the enormous R&D costs of the truly novel CNS drugs which are what we most want to pursue.

This is why many companies have reduced their investment in novel drugs for brain diseases, especially the major psychiatric ones such as schizophrenia and manic-depressive illness. Even those which remain heavily invested realize that they are unlikely to realize any profit from their most innovative drugs in the near term.

But for certain areas, such as Alzheimer's and other degenerative neurologic brain diseases, there is a willingness to take on such a risk because the need is so great. Senior leaders are over the age of 50 and know that without progress in slowing or preventing, for instance, Alzheimer's they stand a 50/50 chance of significant dementia by the time they are 90. Given society's success in treating heart disease and improving success with cancers, maintaining one's health until 90 is within reach for more and more of us but of dubious value if we are demented.

Many have now rallied behind this cause. The NIH, clinical scientists, patient advocacy groups, philanthropies, FDA and industry joined together under the umbrella of a remarkable effort led by the National Institute on Aging. It is called the Alzheimer's Disease Neuroimaging Initiative (ADNI) which, put simply is a collaborative effort to find so-called biomarkers of disease state, progression and drug response.[2] All findings go into the public domain as soon as the data is gathered and processed. This allows for the rapid standardization, quality control and sharing of methods to answer critical questions about patients and treatments as quickly as possible. The ADNI model has taken hold world wide. Currently the European Union, Japan, Australia and Korea have made support to such translational medicine initiatives for neurodegenerative disorders part of their national priority. The US based Alzheimer's Association, a patient advocacy group, has played a catalytic role in coordinating international efforts.[3]

We use the term "translational medicine" to cover all of the science and technology development activities required to take potential drug targets emerging from basic science and validate them as beneficial for human diseases.

---

[2] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, Trojanowski JQ, Toga AW, Beckett L. The Alzheimer's Disease Neuroimaging Initiative. Neuroimaging Clin N Am. 2005; 15(4):869-77, 2005.

[3] Carrillo MC, Sanders CA, Katz RG. Maximizing the Alzheimer's Disease Neuroimaging Initiative II. Alzheimer's Dement 2009; 5:271–5.

And it is an enhanced focus on translational medicine which offers the best hope for more effective application of basic neuroscience to brain diseases.

Public support of basic science through the NIH and other mechanisms has and continues to produce amazing advances. A robust private sector coupled with sophisticated regulatory oversight has delivered a wide range of safe drugs that increase longevity and quality of life. The introduction and use of an earlier generation of new drugs is estimated to account for 40% of the 2 year increase in average US life expectancy between 1986 and 2000.[4] But to realize the promise of more recent scientific advances we must invest much more in the tools of translational medicine, an area which has received much less focus support than basic science at one end or large clinical trials at the other.

The right balance of resources across the domains of basic research, translational medicine and clinical trials has yet to be achieved. And to do this most effectively, we need to expand the "open source" clinical data model pioneered by ADNI. Academic and government scientists, clinicians, drug developers, patients, industry representatives and legislators can work together to create a new paradigm of drug development that recognizes the current state of neuroscience as well as the interdependence across constituencies. We should not expect the paradigms established during the 60's and 70's to be optimal for establishing incentives and processes appropriate to modern neuroscience in the age of the Internet.

1. There are two specific, feasible and implementable initiatives that would pay high dividends in the shortest time. These can deliver because there is already a back-log of to-be-validated targets for brain diseases as well as many pockets of relevant data that are not generally available.
2. Open sharing of all relevant clinical data on characterization of disease state and drug response following proper anonymization to protect individual privacy

Putting the research tools and compounds held by both commercial entities and universities in the public domain ("pre-competitive space") as quickly as possible facilitated by innovative approaches to the Intellectual Property issues

Both of these initiatives require a degree of sharing and working together that is only possible in the age of the Internet and build on models which are already operable in several areas of science and society. When the public/private partnership around biomarkers for Alzheimer's was launched in 2004 many were

---

[4] Lichtenberg FR. The impact of new drug launches on longevity: evidence from the longitudinal, disease-level data from 52 countries, 1982-2001. Int. J. Health Care Finance Econ. 2005; 5: 47-53.

skeptical about the effects of putting clinical research data in the public domain as it was generated. What was then viewed as a risk is now appreciated as a important means of extracting the most information in the shortest time. Furthermore, one opens up the opportunity for a range of analytic approaches that go beyond anything that a single group of investigators could undertake.

The second initiative has been partly pioneered through entities such as the Foundation of the National Institutes of Health (FNIH) where government and industry can interact in a collaborative and "precompetitive" manner.[5] An important focus of the FNIH since 2007 has been to develop biomarkers, the research tools for translational medicine (The Biomarkers Consortium). There are other programmatic examples whereby companies have made compounds available to NIH for exploratory studies in schizophrenia, depression, alcoholism and drug abuse. On the other hand, the degree of academic, industry and government involvement is still tiny compared to the need. Stakeholders from all sectors are in discussions to see how more critical biomarker development can be put in the public domain.[6]

Multiple issues emerge when one brings together philanthropic, scientific , regulatory and commercial entities to invest in a common effort. None of these, however, are show stoppers.[7] Concerns include the potential conflict of interest of academic investigators and institutions as well as the traditional proprietary viewpoints of some. Some might ask, "Why should I pay for something that might benefit the business of other?" This, however, is no longer such a universally shared question from industry. As industry executives tackle the question of how to increase productivity, many recognize that there might be an advantage to having more aspects of drug development in the public domain ("pre competitive space") and operate companies in more of an open network fashion. But, for many, tools and methods are still viewed as intellectual property and know how which should be proprietary so as to protect one from the competition. Thus, the type of sharing involved in the Biomarker's Consortium of the FNIH can be a hard sell and dismissed as foolhardy from a business point of view. Given the expectation that businesses are profitable and deliver to shareholders, these leaders are not wrong to raise questions about sharing tools and methods that might help a competitor better develop its patented compound.

---

[5] FNIH (Foundation for the National Institutes of Health). 2008. *FNIH.* http://www.fnih.org.

[6] IOM (Institute of Medicine). 2008. *Neuroscience biomarkers and biosignatures: Converging technologies, emerging partnerships.* Washington, DC: The National Academies Press.

[7] [7]IOM. 2009. *Venture philanthropy strategies to support translational research.* Washington, DC: The National Academies Press.

Might it be possible to create a set of laws and incentives that would facilitate sharing of the tools so that the real business would be to find the safest and most effective compound for a particular target? So, instead of having industry focusing on whether it can use internal know how to beat someone to the finish line with some particular version of what is essentially the same drug being pursued by several companies, it would compete around who actually has the best compound for an disease. The tools and methods for establishing the characteristics of a drug would be shared by all.

Furthermore, no single entity is large enough to develop and implement all of the sophisticated methods available to explore brain disease and drug treatment. Because any single institution can only focus on selected bits of the millions of data elements generated by modern studies, sharing data will increase the likelihood that important findings well be extracted. It is also possible that by such open sharing one might more readily figure out whether one's patent protected compound does or does not have commercial value. Industry might ultimately benefit more by sharing early clinical data than by trying to work within the silo of a single entity. What is needed is a nuanced set of laws and regulations that provide an incentive for the type of sharing that is certain to advance the field.

In conclusion, we now recognize that the implicit contract between publically funded research, government regulation and private drug development crafted decades ago does not deliver in the era of modern neuroscience. A paradigm shift toward much broader and earlier sharing of clinical data would have an immediate positive impact. A parallel broad collaborative investment in the tools of translational medicine would fill a gap and greatly accelerate the identification of valid drug targets. Innovative approaches to managing intellectual property concerns as well as periods of patent exclusivity should be given serious consideration to facilitate this transition.

Mr. KUCINICH. Your entire statement will be in the record, Dr. Potter.

Dr. POTTER. I would like to mention one thing. We do have an initiative, which Dr. Akil has already referred to, the Foundation of the National Institutes of Health, where we are beginning to try to bring us all together to work in this pre-competitive manner. I want to emphasize that the funding and infrastructure and degree of support to really do it at a proper national scale is simply not great enough.

Mr. KUCINICH. Thank you.

Dr. Coetzee.

STATEMENT OF TIM COETZEE, PH.D.

Mr. COETZEE. Thank you, Mr. Chairman and Mr. Kennedy, for inviting us to speak here. I am honored to be here with these distinguished panelists.

My name is Timothy Coetzee. I am the President of Fast Forward, the venture philanthropy arm of the National Multiple Sclerosis Society.

I am here today on behalf of the estimated 400,000 Americans and the many thousands of veterans who live with MS every day. Together, we ask you to help us advance MS research and really neurological research across the board for all of our colleagues who are affected by neurological disease. We need your help in providing resources and policies to expand collaboration and networks between Government, patient advocates, private foundations and the pharmaceutical and biotechnology industries, and of course, academic investigators.

While my remarks focus on MS, really they can be applied across the board. Multiple sclerosis is a chronic, unpredictable, often disabling disease of the central nervous system. It interrupts the flow of information from the brain to the body and stops people from moving.

MS is the most common neurological disease leading to disability in young adults. But despite many decades of research, its cause remains unclear and there is indeed no cure. While we are grateful for the availability of a number of FDA approved disease modifying therapies, we still need more and better cost-effective therapies. Finding these new therapies hinges on the research and the kinds of collaborative efforts that we are talking about today amongst all the stakeholders.

It has been our experience that research discoveries can happen in a lot of different ways, as you have heard today. Some require lots of careful years of shepherding, while a lot can happen overnight. Whether it is a molecule or a tool, they all need a number of steps to be taken in order to translate those discoveries into actual applications that can be used in people with MS, as well as other neurological diseases. This involves collaborators, commercial development, access to clinical trial participants and a lot of money.

We were created as an organization by the National MS Society specifically to drive commercial development for MS therapies. We have made a commitment to ensure that potential new therapies

actually make it into the clinic and are developed and are able to be used for people with all forms of MS.

We have found that all too often, promising drug treatments languish because companies lack the funding, focus to conduct pivotal research that will break through barriers and move a compound through the development pipeline and ultimately into clinical trials. We fill the gap that is often called the valley of death by creating a collaborative environment between scientists, clinicians, academic researchers and of course, commercial visionaries. By creating these vital networks, Fast Forward increases the focus on MS and speeds the process of bringing drugs to market.

Today we join with our patient advocacy colleagues in calling for more investments and policies to sustain innovation in neuroscience research and development. In our view, expanding and sustaining innovation in neuroscience R&D really requires three critical elements. As you have heard today, we need to sustain a large and vibrant medical research community in the United States. Medical innovation doesn't happen in isolation, it happens amongst a community of scientists and physicians actively involved in understanding knowledge and disease about biology and human disease. It is vital that we continue to expand our commitment to the National Institutes of Health and work also funded through the Department of Defense and the Veterans Administration.

Second, we also believe that we have to create an environment conducive to the formation of what we call fluid networks of scientists engaged in translational research. We know that research and innovation happens faster when scientists work together across networks, fields, institutions, and borders, for that matter. Coordination by the Government agencies, private foundations and patient advocates is critical to ensuring these networks.

And last, we believe that Government, foundations and patient advocates have to use their influence and financial resources to connect people together across sectors. We know from our own experience that young companies and innovators work smarter and faster when you have experts in the private sector working with experts in the academic sector. We need to do more of this, so that all the stakeholders can enhance neuroscience R&D.

In conclusion, Mr. Chairman, the United States has a long history of being a leader and driver of neuroscience research and development. Unfortunately, we do find ourselves in the environment where economic challenges are beginning to threaten this leadership. As patient advocates, we urge action to ensure that there is greater coordination amongst the stakeholders. Every day, Americans receive the diagnosis that they have a neurological disease. These individuals do not have the luxury of time. They need our help to create a research and development environment where they can have access to the best treatments to stop their disease and restore lost function. Thank you for helping us move closer to that world and thank you for your time.

[The prepared statement of Mr. Coetzee follows:]

Testimony of Timothy Coetzee, Ph.D.
Representative of a Patient Advocacy Organization
President, Fast Forward LLC

Committee on Oversight and Government Reform
Domestic Policy Subcommittee
U.S. House of Representatives
Hearing on September 29, 2010

Thank you Chairman Kucinich and Ranking Member Jordan. Thank you members of the Committee. I am honored to be invited to speak here today among many distinguished panelists and to represent patients who live with chronic neurological disease.

My name is Timothy Coetzee, and I am the President of Fast Forward, the venture philanthropy arm of the National Multiple Sclerosis Society. I am here today on behalf of the estimated 400,000 Americans and the more than 20,000 veterans who live with MS and are being treated by the Veterans Health Administration. The number of veterans affected by MS is yet more alarming given that the VA only treats about one-third of our veterans. Finally, I am also here on behalf of the researchers in the United States who are engaged in discovery and development of new treatments and ultimately a cure for MS.

Together, we ask you to help us advance MS research by providing resources and policies that support and expand collaboration between government, patient advocates, private foundations, pharmaceutical and biotech industry and academia.

No Cure for Multiple Sclerosis

Multiple sclerosis is a chronic, unpredictable, often-disabling disease of the central nervous system. It interrupts the flow of information from the brain to the body and stops people from moving. Every hour someone is newly diagnosed. MS is the most common neurological disease leading to disability in young adults. But despite several decades of research, the cause remains unclear, and there is no cure. The research must continue.

The symptoms of MS range from numbness and tingling to blindness and paralysis. MS causes loss of coordination and memory, extreme fatigue, emotional changes, and other physical symptoms. The progress, severity, and specific symptoms of MS in any one person cannot yet be predicted. These problems can be permanent, or they can come and go.

The National Multiple Sclerosis Society recommends treatment with one of the FDA-approved "disease-modifying" drugs to lessen the frequency and severity of attacks, and to help slow the progression of disability. But unfortunately, the cost is often financially devastating. The FDA approved drugs for MS cost more than $30,000 a year, and these treatments continue over a lifetime.

Challenges to MS Drug Discovery

While we are grateful for the availability of seven FDA-approved disease modifying treatments and one FDA-approved symptom treatment, we need better and more cost-effective therapies. Finding these new therapies hinges on research and the collaborative efforts of all stakeholders.

Research discoveries can — and do — happen in a variety of ways. Some require years of careful shepherding, while some can seemingly happen overnight. Whether it's a molecule that could have potential as a new drug therapy, or a tool that can better track clinical trial results and make them move more quickly — each relies on crucial steps that must be taken in order to translate these discoveries into available treatments for people with MS.

Those many steps involve collaborators, commercial development resources, access to clinical trial participants, and obviously considerable financial resources. Progress in treatments for people with MS happens when the greatest numbers of researchers are working on the greatest volume of potential discoveries in the field of MS. We know all too well that promising research from the lab can often be applied to multiple diseases, and that researchers are forced to choose those with money, resources, and commercial potential. This means that in the past, promising therapies with potential in MS have never even made it into the commercial MS pipeline. There wasn't enough return on investment to make MS an attractive first choice.

Unfortunately this is true of many neurological diseases, not just MS.

Role of Patient Advocacy Organizations in Drug Discovery and Development

Fast Forward was created by the National Multiple Sclerosis Society specifically to drive investment into the commercial development of MS treatments and therapies — creating an investment that works for

everyone affected by MS. Like other patient organizations such as the Michael J. Fox Foundation for Parkinson's Research and the Alzheimer's Drug Discovery Foundation, we have made a commitment to ensure that potential new therapies have an opportunity to be developed for people with MS.

Too often, promising drug treatments languish because companies lack the funding or focus to conduct pivotal research to break through the barriers, move the compound through the development pipeline, and ultimately to the clinical trials needed to develop new MS therapies.

Fast Forward addresses this critical gap by providing seed money to academic groups and emerging biotechnology and pharmaceutical companies involved in drug research and development.

Fast Forward further fills the gap, often referred to as the 'Valley of Death' by creating a collaborative environment between scientists, clinicians, academic researchers and commercial visionaries. By creating these vital connections between the research, clinical trial and business communities, Fast Forward increases the focus on MS, further

speeding the process of bringing drugs to clinical trial. As a catalyst for collaboration, Fast Forward identifies emerging challenges, shapes research agendas and finds new opportunities for drug development in MS.

Sustaining Innovation in Neuroscience Research and Development

Fast Forward's story is not unique. Our peers at the Michael J. Fox Foundation for Parkinson's Research, the Alzheimer's Drug Discovery Foundation to name but two are engaged in similar important work to address neurological disease. Together we join with many other patient advocates calling for investments and policies to sustain innovation in neuroscience research and development.

In our view expanding and sustaining innovation in neuroscience research and development requires three critical elements.

First, we need to sustain a large and vibrant medical research community in the United States. Medical innovation requires a community of scientists and physicians actively engaged in pursuit of knowledge and understanding about basic biology as well as human disease. A vibrant research community generates a plethora of often

unconnected ideas which form the basis of medical innovations. Government funders such as the NIH, the Department of Defense, patient advocates, pharmaceutical companies, and other funders play a vital role in sustaining the neuroscience research community. It is vital that we continue and expand our commitment to fund basic and disease research funded by the NIH and programs at the Department of Defense, such as the Multiple Sclerosis Research Program (MSRP) within the Congressionally Directed Medical Research Programs (CDMRP). Without these investments, we will likely miss out on important innovations that could improve the lives of people with neurological disease.

Second, we must create an environment conducive to formation of fluid networks of scientists engaged in translational research. We know from our experiences at the National MS Society and Fast Forward that research and innovation happens faster when scientists, technologists, and translators, my term for people who take the basic lab discoveries and turn them into a drug, work together in networks across fields, institutions, and borders. Through these networks, ideas can be shared and linked together with other insights in order turn innovations into actual therapies. The key to success is that the

research networks are fluid and can adapt by adding new members, going in new directions based on results and so forth. Coordination by government agencies, private foundations and patient advocates is vital to ensuring that researchers are able to form these fluid innovation networks.

Third, government, private foundations, and patient advocates must use their influence and financial resources to connect innovators across sectors. At Fast Forward we serve this role by using our financial resources and influence to connect our portfolio companies with expert scientists in academic research centers. We know first-hand that young companies are able to work smarter and faster when they are working with established MS experts rather than trying do the work on their own. All of the stakeholders must do more of this in order to enhance and expand neuroscience research and development.

In conclusion Mr. Chairman, the United States has a long history of being a leader, indeed a driver, of neuroscience research and development. Unfortunately, today we find ourselves in an environment where economic challenges threaten our leadership in

this area. As patient advocates, we urge action to ensure that there is greater coordination among the stakeholders so that we can remain a leader in neuroscience research and development. Every day Americans receive the news that they have a neurological disease. These individuals do not the luxury of time. They need our help and we can do that by creating a research environment conducive to discovery and development of breakthrough treatments that stop their disease and restore lost function.

Thank you for helping us move closer to a world free of MS, and thank you for your time.

Mr. KUCINICH. Thank you very much.
Dr. Parker.

STATEMENT OF KEVIN KIT PARKER, PH.D.

Mr. PARKER. Chairman Kucinich, Congressman Kennedy, thanks a lot for inviting me here.

I am going to tell you the story of TBI through a rather uncommon lens, because I am a soldier and a scientist. I am going to start last year, last March in the Tangi Valley in Afghanistan. You will see it up there. We ran a patrol and the lead vehicle, we had been fighting since off and on since about 8 a.m., we hit an IED. We flipped over the MRAP and there you see us running up to check the soldiers.

About 30 seconds after this photograph was taken, an RPG hit that cliff right above our heads, when we were trying to pull the wounded soldiers out of there. And then the day got a lot worse.

That just kind of illustrates the situation you were talking about, combat stress. There is a lot to that, and we could talk more about that later. But this kind of illustrates what is happening out there in the battlefield. This is the ignition event for TBI, and it is the ignition event for those neurodegenerative diseases that can result on down the road.

So if you will move to the next slide, please. I want to just teach you a little bit about TBI, and I can only teach you a little bit, because I am not a neuroscientist. I was doing the heart when someone started to kill my friends with IEDs, and I figured I had better get a piece of this fight.

So if you take a look, you imagine that the whole patient, the soldier, the behavior, those functional behaviors that can arise from neurodegenerative diseases, that is a meter link scale. What happens when that IED goes off? The brain, listed up there at the top of that scale gets slammed forward into that skull because that shock wave couples into the body. And it starts a cascade of injuries that goes from the centimeter scale of this brain through the neural networks that allow you to recognize a friend, speak to a loved one, count your change at the Burger King. It disrupts the neurons, breaks the synapses, all the way down to the nanometer scale at the bottom, where you see endocrine bonding, cellular matrix, this is where mechanical forces get transduced into physiological signals called mechanical transduction pathways. In this case, it is a pathophysiological signal, because we are activitating signal pathways that we don't necessarily want to activate.

This is the temporal scale of TBI. I am going to look mostly on this time line to the right of the blast, what we call right of the boom. You can assume that prior to the blast, we assume we get stable neural structures, stable vascular structures and a stable gene expression. There is a big asterisk next to that, because these guys are in combat, they are facing physical danger, moral jeopardy. There is a lot of stress hormones there. We don't know exactly how they might be impacting all those structures.

Once that boom happens, things start happening on a nanometer scale. Proteins undergo conformational changes that turn on those signaling pathways that cause excitotoxicity that cause these neurons to have their membranes torn, to activate signaling pathways

in mild cases of TBI that you might not see for some time. You can't diagnose them currently.

If you follow that time line going all the way across to the right, spanning out through the rest of the epidemiological life span of that soldier, you are going to see a variety of problems emerge. They might not emerge right away, but eventually they might. And when they do emerge, every time they emerge, if it is 20, 30 years on down the road, that is one more victory for the opponents that we are facing on the battlefield. When they take another soldier down with Parkinson's disease or Alzheimer's or dementia on down the road, they are still winning that fight.

We talk about counterinsurgency as a long war. Taking care of these casualties is the longer war. What we need to do is develop a cohesive plan to address this longer war. It is interagency, just like we have on the battlefield right now. But interagency, just like you heard from the first panel, is the only way we are going to solve this problem.

I want to make a couple of recommendations before I close here. When you start taking a look at putting people onto this problem, I think as an outsider coming in, there is a need to evangelize the scientific community about TBI. We talk about job retraining for people that have been in textiles, that have been in the automotive industry that need a new job, we need retraining for scientists who want to come into this field, who want to make that jump, it is very difficult for them.

So this might be as simple as running courses at the Marine Biological Lab at Woods Hole, MA, or Cold Spring Harbor Labs in New York. It could be as simple as that. It could be something more complex, where NINDS, VA, DOD and NIMH get together and start talking about that kind of job retraining. That is literally what it is.

We need funding mechanisms for a long, sustained interdisciplinary effort. Earlier you heard about the prosthetics programs being run out at DARPA. The program manager for that is Geoffrey Ling, who is the only neurointensive care doc in the Army. He is also the program manager for my DARPA funding, the TBI program called PREVENT, Prevent an Explosive, Violent Neurological Trauma. You have one guy doing this thing all by himself over there at DARPA.

But these kind of interdisciplinary fights, where you need people that understand shock physics, cell and tissue mechanics, molecular biology, neural biology, psychiatry, that is very complex. And you probably won't find an instance in American or scientific history where all those scientists have been represented in the same room at one time. About the only people that can pull that together is DARPA.

But DARPA does short-term funding. They come in, they impact a field and they move on and let another agency pick it up. We need a longer term, more sustained effort at bringing these people together for a long time.

I think that two things need to happen in terms of establishing goals for this field. One is, I am not going to surrender that turf that you see just to the right of boom. Right now, if you get a mild TBI on the battlefield, you might get treated, you might get evalu-

ated, you might get pushed back into the fight. And one of the soldiers that was in that photograph I showed you earlier in that photograph has been blown up 10 times between tours in Iraq and Afghanistan. What is going to happen when he goes home 1 day and he suddenly can't remember his son's name? That is a victory for the enemy.

I am not going to surrender that turf to the enemy. If you take a look, just to the right of boom, when I run up there and I take care of that soldier, when I pull open that MRAP door to see if he is OK, the treatment for that TBI needs to start right now. So one of the goals that we need to have for this interdisciplinary research program is to develop a technique or a means of treating prophylactically the neurodegenerative diseases that might not emerge until 20 or 30 years on down the road.

The second thing we need, and this is something that was mentioned previously, is we need a Framingham heart study on TBI. It might be PTSD, too. But the DOD and the VA keep great medical records. I live in Massachusetts. The Framingham heart study run by Boston University has revealed all kinds of great things about heart disease that scientists like me, who traditionally work in the cardiac field—now I split my time between TBI and the heart—have used to guide our scientific studies. We currently don't have that data base. We need that data base.

A Framingham heart study, and short-term goals, so that over entire timeframe of the disease, and that is what TBI is, it is a disease, we need opportunities, we need funding, we need organization and we need leadership to do that.

In conclusion, I would like to thank you again for the opportunity to testify.

[The prepared statement of Mr. Parker follows:]

Testimony

of

Kevin Kit Parker

Thomas D. Cabot Associate Professor of Applied Sciences

Associate Professor of Biomedical Engineering

Harvard University

Before the

Committee on Oversight and Government Reform

Domestic Policy Subcommittee

United States House of Representatives

September 29, 2010

Mr. Chairman, Ranking Member Kucinich, and distinguished Members of the Committee, thank you for inviting me to testify here today. I am the Thomas D. Cabot Associate Professor of Applied Sciences, Associate Professor of Biomedical Engineering at the School of Engineering and Applied Sciences at Harvard University, with core appointments in the Wyss Institute for Biologically Inspired Engineering, the Harvard Stem Cell Institute in Cambridge, Massachusetts. In addition to these responsibilities, I am a Major in the Rhode Island Army National Guard and have completed two combat tours in Afghanistan with the 82nd Airborne and 10th Mountain Divisions.

I have degrees in engineering and physics and additional postdoctoral training in biomedical engineering and pathology. My research at Harvard has been focused on understanding how cells in the heart build themselves and tissues and how the violation of their structure-function relationships results in heart disease. However, since my first tour in Afghanistan in 2002-03, the threat of improvised explosive devices (IEDs) on the battlefield has consumed an increasing amount of my efforts in my laboratory and in my external work as an consultant to various agencies associated with the DoD concerning themselves with the IED problem . At Harvard now, one third of my ~20 member research team is focused on some aspect of blast-induced traumatic brain injury, known most commonly as TBI.

By virtue of my experience on the battlefield and in the laboratory, I want to tell you the TBI story as I see it, a battlefield to bench perspective. We can start on March 22 2009 in the Tangi Valley of Afghanistan where I was patrolling with a Route Clearance Platoon 13, a group of combat engineers, explosive ordinance experts, IED experts, and myself representing the Center for Army Lessons Learned at Ft Leavenworth, KS. Our first firefight that day had occurred at about 8 AM in the eastern end of the valley in Logar Province and as we approached the western end in Wardak Province, we were subjected to a complex ambush where our lead vehicle was flipped by an IED of approximately 500 lbs of homemade explosives (Fig. 1). When myself and a squad leader, that I will refer to as *Joe* for reasons to be discussed later, dismounted our vehicle to move forward to check for casualties, we received fire in the form of rocket-propelled grenades and small arms from multiple directions. With the road blocked by our overturned vehicle, casualties in the first vehicle, we were pinned against a cliff wall taking fire from

our 9 o'clock position in the valley floor. Eventually the enemy would attempt to flank us at the front and rear of the convoys. Joe ran back and forth along the one lane valley road, under fire, to coordinate the movement of casualties from our forward, disabled vehicle to vehicles he guided forward during the firefight. The four casualties included one soldier with broken vertebrae, another with facial and extremity injuries, and all four suffering TBI to varying degrees. After artillery fire missions and rotary wing close air support, we gained control of the situation and evacuated our casualties and after staying the night in the position, the next day recovered our vehicle and moved out of the Tangi.

Fig. 1. March 22, 2009, ~1700 hrs local time, Tangi Valley Afghanistan. Lead vehicle in RCP 13 route clearance convoy is hit with a 500 lb IED of homemade explosive. Dismounted soldiers in the photograph are recovering casualties from the vehicle. Approximately 2 minutes after this photograph was taken, an RPG hit the cliff wall above the cab of the overturned vehicle, initiating a firefight.

So four soldiers with TBI that have to be treated and should be monitored for life. But I am also worried about Joe and the others like him. In this case, Joe is an old school noncommissioned officer, a seasoned veteran of multiple tours in Iraq before he came to Afghanistan. All on route clearance teams, including the tour in Afghanistan he has been blown up nearly a dozen times at this point, sometimes in a vehicle, sometimes on dismounted patrols. He complains of headaches, trouble sleeping, and other symptoms commonly associated TBI. However, he considers himself still mission capable. Awarded a Bronze Star with V-device that day in Afghanistan, he is somewhere, right now, working some part of this war.

What is TBI?

Traumatic brain injury is brain trauma and can range from a concussion to a penetrating head wound. The scales of the injury can be intimidating. Figure 2 illustrates the spatial scales of the brain, from the nanometer-size proteins, integrins, that traverse the lipid membrane of neurons, brain cells, connecting the extracellular matrix proteins to the intracellular architecture of the neuron, up to the micron scale of the synapse, the chemical information junction between two communicating neurons, to the millimeter and centimeter length scales of the neural networks that allow us to calculate our change at the cash register, recognize a friend, speak, see, and smell. Considering the whole Central Nervous System to include the

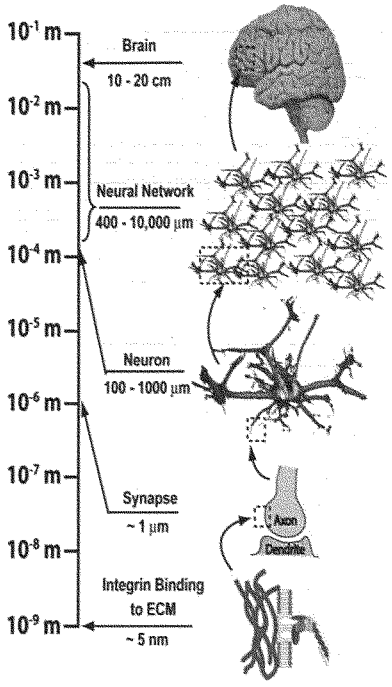

Fig. 2. Spatial scales of interest in the TBI problem, from the integrin proteins that mechanically stabilize neurons to the brain.

brain and spinal cord, we are talking about a spatial scaling problem of nine orders of magnitude.

But it is the temporal scaling problem that most clearly illustrates the TBI problem. In Fig. 3, I want to draw your attention to the right side of the timeline, what we call "right of boom". What I have tried to do in this figure is capture the range of physiological changes that are occurring as the blast wave propagates into the skull and then over the lifespan of the patient.

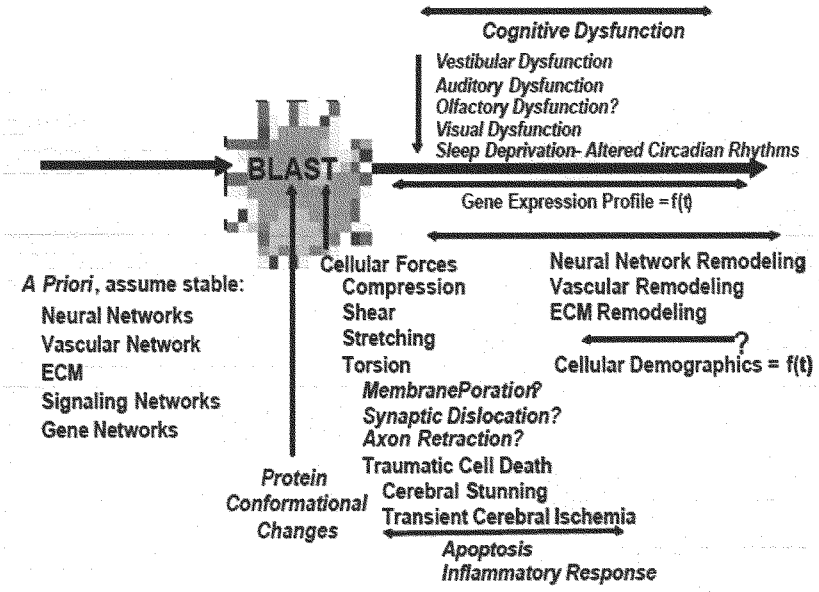

Fig. 3. Timeline of blast-induced traumatic brain injury covering nanometer to meter length scales of the blast wave coupling into neurons, to the behavioral issues these patients suffer, this schematic is the sequelae of a laundry list of neurodegenerative diseases that may develop from TBI, including Alzheimer, Parkinson's, and Lou Gherig's disease.

The events depicted are not exclusive to blast-induced TBI (bTBI), they represent all brain trauma. It is important to note that diseases such as Alzheimer's, Parkinson's, dementia pugilistica, and the most recent report out of the Veteran's

Administration that suggested that amyotrophic lateral sclerosis, commonly known as Lou Gehrig's disease, may be linked to brain trauma are all consequences of what you see on the timeline to the right of boom. So it is important to consider TBI as an ignition event for the pathological cascades that lead to the diseases that we might not recognize until we are far to the right of boom. And to date, most of our research, is probably to the far right of boom for TBI and the neurodegenerative diseases that result from it.

So what are we going to do about Joe? What are we doing for Joe?

I am not a TBI or brain expert, but a few years ago, after assessing the problem and the scientific literature, I thought I identified an angle on the problem that was within my research team's expertise. Initially, the effort was funded by Harvard's endowment and myself. Without preliminary data, with no publication track record in the field, and little concerted effort to fund TBI research, traditional funding avenues bore little likelihood of success, where my knowledge of IEDs from Afghanistan and my civilian advisory work may not compute in a typical biomedical grant review process. I was, however, able to get funding from the Defense Advanced Research Projects Agency, DARPA, thru a program called PREVENT, PREventing Violent Explosive Neurologic Trauma headed by an Army neurointensivist, COL Geoffrey Ling, PhD, MD. I would imagine that at DARPA, my downrange experience could be computed along with my scientific expertise in what might be the most complex, interdisciplinary problem to face medical science in its history.

The problem is complex because across the temporal scale of events, it can require a knowledge of explosives, shock physics, cell and tissue mechanics, molecular biology, neurobiology, psychology, and neurodegenerative diseases. I am not an expert in any of these fields, but I know a few words from each and that might be about as good as it gets.

Barriers to Traumatic Brain Injury Research

As an outsider to neuroscience and the TBI problem, I see several barriers to launching a full spectrum attack on the problem of TBI:

A. A lack of awareness within the scientific community. *Recommendation: Funded efforts to evangelize the neuroscience and cell engineering fields about TBI, such as funding one week courses on TBI science at the Marine Biological Laboratory at Woods Hole MA, or at Cold Spring Harbor Laboratory in New York*

B. As I mentioned, a lack of scientific talent trained broadly across a range of fields that have probably never been well represented in the same room unless DARPA is hosting. *Recommendation: DoD predoctoral and postdoctoral fellowship program specifically for students and trainees working in the TBI field, or entering the field*

C. Lack of funding mechanisms for long, sustained, interdisciplinary efforts. We speak of counter-insurgencies like what we have faced in Iraq and Afghanistan as the *Long War*. For those soldiers suffering TBI, their war is going to be a lot longer than the Long War, the *Longer War* if you will. *Recommendation: See later discussion of a full spectrum, interagency effort*

D. Lack of *in vitro* experimental models for basic research and drug discovery. *Recommendation: Specific funding programs to develop technology for bench top research and high thru put screening assays of potential TBI therapeutic opportunities*

E. A hesitancy to do the kinds of unpleasant animal experiments that are going to have to be conducted to understand the disease, identify therapeutic opportunities, and then test them prior to treating patients. *Recommendation: Get the government laboratories to host core facilities to support animal experiments conducted by university or industrial researchers. Actively seek and prosecute animal rights groups that intimidate researchers in this field.*

F. A lack of interagency cooperation and leadership. *Recommendation: An interagency task force composed of representatives from DoD, VA, HHS,*

and Energy, reporting directly to the Vice President, or bipartisan leadership team, on synchronized efforts across the spatiotemporal scales of the problem.

The Longer War: Caring for the Chronically Wounded Warfighter with TBI

In the Golden Hour, the first hour after a soldier has become wounded, we know that immediate medical care can increase his or her odds of survival significantly. What we don't know if what kind of Golden Hour intervention may prevent a neurodegenerative disease. *A goal of our research should be to identify a therapeutic opportunity where we can initiate a prophylactic course of treatment at the time of injury to prevent a neurodegenerative disease 10, 20, or 30 years down the road.* This challenge will focus the scientific effort on identifying the precise mechanisms of injury, the signaling cascades that might be vulnerable to therapeutic exploitation, and candidate molecules.

The Golden Hour is the first chapter in the *Longer War* of caring for these casualties. With each diagnosis of a neurodegenerative disease amongst a TBI soldier in the decades to come, our nation's enemies win again. We need to exploit the ability of the DoD and the VA to maintain detailed personnel and medical records to start a study similar to the Framingham Heart Study to monitor soldiers, both brain injured and not, over the course of their lifespans. Like the Framingham Heart Study run by Boston University in the town of Framingham, MA, we can register data gathered prior to injury with post-injury data to do detailed, longitudinal studies of how TBI evolves into neurodegenerative diseases like Alzheimer's and Parkinson's, understand who is most vulnerable, and determine what courses of treatment work. *A goal of our research should be to identify the relationships between TBI and long term outcomes after diagnosis of Alzheimers, Parkinson's, and other neurodegenerative diseases.* There is no substitute for these kind of studies as far as the scientific community is concerned. Scientists need this data to effectively, and efficiently, evolve therapeutic options.

Who Should Lead the Longer War?

TBI is not a soldier problem and for many in the field, the perception is that NIH considers it DoD's turf. This perception is best corrected by mandated collaboration between DoD, the VA, and HHS on this problem. This will have to be an interagency effort building on NIH's success with vetting competing hypotheses against each other. A good example of the NIH's success is the 'Big Tent' strategy taken by the NCI on the war on cancer. This success must be replicated.

It is important that the epidemiological data available from the DoD and VA be made broadly available to the civilian scientific community in a form that is amenable to statistical analysis, protects national security interests, and used to guide scientific inquiry. It is important to mass as much scientific talent on this problem as possible, and to do it as soon as possible. Interagency tribalism will inhibit progress, as will competition amongst patient advocacy groups that perceive NIH budgets as a zero sum game. Agencies with special talents for running complex, multidisciplinary efforts should be encouraged to take an active role in coordinating this effort. Finally, the leadership of such an effort should be unfettered by political or departmental affiliation.

CONCLUSION

In closing, thank you again for the opportunity to testify here today about my perspectives on the TBI problem. I, speaking for the community of scientists working on TBI, will continue to pursue an understanding of this disease and its role in the genesis of other neurodegenerative diseases more commonly known to this committee. As a soldier and as an officer responsible for the well being of my troops, the weight of responsibility I personally feel in regards to this problem cannot be overstated. What I, and others, need to accomplish this mission, to win this part of the war, is a concerted effort on the part of the USG to choreograph assets and efforts across the various stakeholder agencies for an effort that will lead to the successes seen in the War on Cancer, declared in the 1970s. A Big Tent

strategy, where all who have a piece of this fight are welcome, is the best means of accomplishing this end.

Bibliography

Ling G, Bandak F, Armonda R, Grant G, Ecklund J. Explosive blast neurotrauma. J Neurotrauma. 2009 Jun;26(6):815-25.

National Institute of Neurological Disorders and Stroke. NINDS Traumatic Brain Injury Information Page. http://www.ninds.nih.gov/disorders/tbi/tbi.htm, accessed 27 Sept 2010.

Dekosky, S.T., Ikonomovic M.D., Gandy, S. Traumatic Brain Injury – Football, Warfare, and Long-Term Effects. New England Journal of Medicine 2010 E-pub 22 September.

Johnson V.E., Stewart W., and Smith D.H. Traumatic brain injury and amyloid-B pathology: a link to Alzheimer's disease? Nature Reviews Neuroscience 2010 11:361-370.

Mr. KENNEDY. We need your leadership. Kevin, awesome. Thank you for your service, every which way.

Mr. KUCINICH. Dr. Morrison.

STATEMENT OF JOHN MORRISON, PH.D.

Mr. MORRISON. I would also like to thank the chairman and Mr. Kennedy for the opportunity to be here today to discuss the potential and promise of neuroscience.

I am here today on behalf of the Society for Neuroscience, which is a non-profit membership organization of more than 40,000 basic scientists and clinicians from around the world who study the brain and central nervous system. Our members work across the entire research spectrum to advance basic understanding of brain function and to translate basic science discoveries into treatment strategies for more than 1,000 brain illnesses.

Exciting achievements in scientific discovery have fueled tremendous progress over the last decades, positioning the neuroscience community for transformational progress, thanks to new tools and technologies that enable us to study the brain as never before. You have heard about some of those today.

Today I would just like to offer two brief examples of emerging discoveries that hold promise for research and the American people. First, neuroscientists are making great strides in understanding the brain circuits involved in PTSD and how these circuits are altered by stress. We know now of a number of altered brain chemicals and systems associated with PTSD and the part of the brain that links learning and memory to emotion is smaller in people with PTSD. As Mr. Kennedy pointed out earlier, PTSD is circuit-based, specific circuits are malfunctioning.

Neuroscientists are also making tremendous progress in understanding the neurobiology of aging. We know that a part of brain cells called spines in the prefrontal cortex are depleted as we age, and this leads to cognitive decline. These basic research findings have already provided scientists and clinicians with new therapeutic targets to prevent the loss of spines and retain cognitive health. These same observations will help form a new approach to therapeutics for Alzheimer's disease.

The importance of neuroscience research is reflected, and you have heard about this already today, in the fact that brain and nervous system disorders result in more hospitalizations than any other group, affecting more than 50 million Americans a year at costs exceeding $460 billion.

A strong investment in basic science innovation is also critical to our national economy. It creates thousands of high-wage jobs at a critical time.

Biomedical research must be seen as one primary solution for diseases and disorders that already cost society hundreds of billions of dollars a year, several of which increasingly threaten our social fabric, including my area of expertise, Alzheimer's disease. Two years ago, the bipartisan Alzheimer's Study Group, co-chaired by Newt Gingrich and Bob Kerry, painted a very troubling picture of the social impact of Alzheimer's disease, if we don't do more to delay or prevent progression of the disease.

The outlook for Alzheimer's is not morally sustainable for those millions who we know will suffer terribly or for their families. Nor is it economically sustainable for our Nation. The situation is repeated for a thousand other brain disorders. At a time of economic challenge for our Nation, the economic question is not, how can we afford to invest in research, rather, it is how can we afford not to invest in research that has the potential to save many times the dollars invested.

The issue discussed today remind us that scientists and medical practitioners must be much more engaged in a two-way dialog if we are to ensure that discoveries translate into treatments and clinical observations are integrated into research development. We have seen this referred to several times today.

Neuroscience research that benefits one condition or disorder has broad potential applications for many conditions, making it critical that we encourage more collaboration that crosses traditional scientific boundaries. One of the most critical collaborations is across what has traditionally been thought of as two largely independent enterprises: basic science and clinical research. In fact, we must recognize that both endeavors are necessary components of a continuum that leads to translation. We must encourage and facilitate scientists and clinicians to work together as a team to translate scientific knowledge and discoveries into specific personalized approaches to diagnosis, treatment and prevention of disease.

One example of the importance of practical scientific application and translation is our increased understanding of synaptic plasticity, which is in essence the brain's ability to modify neural circuits to better cope with new circumstances. This incredible capacity for adaptation is a fundamental property of the synapse and our understanding of it emerged from basic science. Yet it is already having a revolutionary impact on therapeutic strategies for multiple brain disorders.

In closing, we live on the forefront of an era of breathtaking potential to advance biological knowledge and human health. Our future success will depend in large measure on sustaining the strong investment in basic neuroscience discovery as well as team-oriented, collaborative approaches between the basic researchers and the clinical researcher.

I look forward to the road ahead in this exciting field and what our success stories will mean to the American people.

[The prepared statement of Mr. Morrison follows:]

Public Witness Testimony
John H. Morrison, Ph.D., Society for Neuroscience
Before the House Committee on Oversight and Government Reform
Subcommittee on Domestic Policy

Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to testify, and for the committee's interest in neuroscience research and development. I am John H. Morrison, PhD, the Dean of Basic Sciences and the Graduate School of Biological Sciences at Mount Sinai School of Medicine in New York City. I am here today on behalf of the Society for Neuroscience (SfN), where I am currently Chair of the Public Education and Communication Committee, and an incoming member of the Society's Council, its board of directors.

It is an honor to be here to discuss the potential and promise of brain research and to update the subcommittee on emerging discoveries and opportunities for greater collaboration. I will also discuss briefly why the nation, and the world, must make aggressive investment in brain research a top priority in coming years given looming health and economic trajectories that are potentially devastating.

About SfN

The Society for Neuroscience is a nonprofit membership organization of more than 40,000 basic scientists and clinicians in more than 80 countries who study the brain and central nervous system. Our members work across the entire research spectrum to advance basic understanding of brain function and how it goes awry, and are engaged in a broad range of scientific research endeavors aimed at understanding, treating and preventing disorders of the brain and nervous system. They also facilitate the translation of basic science discoveries into treatment strategies for more than a thousand illnesses ranging from Alzheimer's to autism and attention deficit disorder; from multiple sclerosis to mental illness; from vision and hearing loss to paralysis or limb loss; and from post traumatic stress disorder (PTSD) to traumatic brain injury (TBI). Our researchers are also deeply engaged in understanding the roots of healthy human development, healthy aging, stress, obesity, and other conditions that affect or promote brain wellness. Neuroscience is a broad and deeply interdisciplinary field, relying on crucial advances in physics, computer science, mathematics, chemistry, engineering, and basic biology to develop new tools and techniques for studying brain cell activity and behavior.

In pursuit of its mission, SfN provides the world's largest venues for emerging brain science discovery, including hosting one of the world's largest annual scientific meetings, with more than 30,000 attendees, and publishing the broadest and most comprehensive neuroscience journal in the field with more than 15,000 pages of groundbreaking science per year. SfN also provides professional development activities and resources for neuroscientists at all career stages; promotes public information and education; and informs policymakers about knowledge resulting from neuroscience research and implications for public policy and continued scientific progress.

Founded in 1969, the Society's rapid growth today reflects the progress, promise, dynamism, and growing interest in the field. Today, the fastest growth has been among students and international

members, and these are vital and encouraging trends as they represent a strong pipeline of young talented scientists and strong partnerships for continued scientific collaboration.

The Achievements and Future Promise of Neuroscience

America's neuroscience research enterprise has already demonstrated it is a proven pathway to improved health for millions of Americans, better scientific knowledge for human kind, and a stronger economy in hundreds of communities. While we have much farther to go, neuroscientists have made tremendous progress in the understanding and treatment of diseases and disorders. Among other progress, we have emerging genetic or bioengineered treatments for vision and hearing loss; deep brain stimulation for Parkinson's and its promise for other disorders; new understanding of the brain circuitry involved in major mental illness; knowledge of how memories are formed and lost; as well as progress on the genetic contribution to many disorders, as well as emerging biomarkers for many of them as well.

Based on these advances, the neuroscience community today is on the cusp of making transformational progress thanks to new tools and technologies that enable us to study brain function at the cellular, molecular and genetic levels as well as in the living brain as never before. Aggressive and sustained investment in neuroscience is among the most pivotally important components of progress for the 21st century, and it will ensure that we capitalize on the investments and discoveries over past decades.

Today, I offer just two examples of emerging discoveries that hold promise for research and the American people:

Post Traumatic Stress Disorder (PTSD)

A recent study conducted by the RAND Corporation found that an estimated 20 percent of returning service members who served in Iraq and Afghanistan report symptoms of PTSD or major depression. Basic scientific research taking place over the last two decades has significantly contributed to our understanding of PTSD as a serious brain disorder with biological underpinnings. Neuroscientists are making great strides in understanding the brain circuits involved in this complex disorder and how these circuits are altered by stress. For example we now know of a number of altered brain chemicals and systems associated with PTSD including the presence of higher levels of norepinephrine in the brains of PTSD patients; and the part of the brain that links learning and memory to emotion appears to be smaller in people with PTSD. As a new generation of U.S. service members return home from the wars in Iraq and Afghanistan after prolonged exposure to combat-related stress and trauma, the importance of linking basic scientific research findings to clinical innovation is critical to service members, their families, and their caregivers.

The Aging Process

Neuroscientists are also making tremendous progress in better understanding the neurological components of the aging process. We now know that a part of brain cells called spines are depleted as we age, resulting in declines in cognition in the parts of the brain associated with higher levels of learning. These spines are linked to an important class of synapses involved in learning, and many of the synaptic molecules required for this

process have been identified. These basic research findings provide scientists and clinicians with new therapeutic targets to help prevent the loss of function, now that we have identified which spines are lost as we age and their impact on cognition. Neuroscientists have also discovered that the biological events that lead to age-related cognitive impairment are not inevitable. These findings will allow for the development of prevention strategies, while also establishing a foundation for therapeutic tools to reduce cognitive decline through pharmaceutical and lifestyle interventions. Such progress on cognitive aging will surely impact the greatest of all burdens associated with aging and Alzheimer's disease.

These promising discoveries are made in part because, as you heard on today's first panel, neuroscience has a strong partner in the United States federal government. Indeed, we are deeply grateful and proud that America has helped propel the progress of this field through funding at the National Institutes of Health, the National Science Foundation, Department of Defense, Department of Veterans Affairs, and many other institutions that have fueled tremendous progress in diagnosing and treating neurological disorders.

The Importance of Neuroscience Research

Health and disease

In the United States, the more than 1,000 disorders of the brain and nervous system result in more hospitalizations than any other disease group, including heart disease and cancer. Neurological illnesses affect more than 50 million Americans annually, at costs exceeding $460 billion. In addition, mental disorders, excluding drug and alcohol problems, strike 44 million adults a year at a cost of some $148 billion. As has been noted today, neurological and psychiatric conditions will also be hallmark wounds of this era's returning veterans. PTSD, TBI, limb loss, sight and hearing impairment are all major consequences of today's battlefield. The World Health Organization (WHO) reported in 2007 that an estimated 1 billion people suffer worldwide from neurological diseases and disorders, causing 6.8 million deaths annually. Mental health conditions affect millions of people in the world, with WHO estimates of 151 million people suffering from depression, 26 million from schizophrenia, and 125 million from alcohol use disorders. And because many brain diseases affect individuals in their prime earning years, and not just the elderly, the cumulative impact of brain diseases on economic productivity is very significant.

Economic Impact

Finally, In addition to increasing knowledge and identifying new promising health outcomes, a strong investment in basic scientific innovation is also critical to our national economy. First, it is helping to generate economic activity nationally and at the local level, creating thousands of high-wage, high-tech jobs and sectors at a critical time for our economy and the U.S. biomedical research industry. Second, a continued focus in basic science will help ensure that the U.S. remains the world leader in biomedical research. Even as SfN collaborates with global partners, we recognize that strong U.S. leadership is crucial to helping to advance groundbreaking research around the globe while protecting our nation's future. The neuroscience community feeds our nation's larger innovation and R&D pipeline, making our nation the most highly regarded engine of innovation in the world. However, there is growing global competition to lead

this innovation race, and while competition enhances outcomes, we all agree that a strong and vibrant US science and technology sector is vital to the country and the globe.

Finally, from an economic perspective, biomedical research must also be seen as one primary solution for diseases and disorders that already cost societies hundreds of billions of dollars a year, several of which increasingly threaten our social fabrics. One need not look any further than my area of expertise, Alzheimer's disease, to see this fact in stark relief. Two years ago, the Alzheimer's Study Group, co-chaired by former Speaker Newt Gingrich and former Senator Bob Kerrey and comprised of bipartisan policy and science leaders, painted a stark and troubling picture of the social impact of Alzheimer's disease if more progress is not made to delay or even prevent progression of the disease. It reported that Alzheimer's disease afflicts more than 5 million Americans and is already the nation's third most expensive disease, not even counting more than 94 billion hours consumed annually in uncompensated caregiver assistance. Unchecked, Alzheimer's cases will increase by more than 50 percent in 20 years and double again to as many as 16 million cases by 2050. This will result in disease-related costs to Medicare and Medicaid alone of $20 trillion in constant dollars over 40 years, rising to over $1 trillion per year by 2050.

The outlook for Alzheimer's is not morally sustainable for those millions who we know will suffer terribly, or for their families. It is also not economically sustainable for our nation or other aging nations around the world. And this situation is repeated for more than 1,000 other brain based disorders as populations grow and age. At a time of economic challenge for our nation, the economic question is not "how can we afford to invest in research." Rather, it is "how can we afford ***NOT*** to invest in research that has the potential to save many times the dollars invested."

The Neuroscience Challenge: Science and its Service for Health

In my view, the basic science findings discussed today, and their vital clinical and societal impact, remind us that scientists and medical practitioners must be much more engaged in two-way dialogue if we are to ensure discoveries translate into treatments and that clinical observations are integrated into research development. Additionally, neuroscientists know more than ever about the interaction and interconnections between brain anatomy, functions, and disorders. Thus, neuroscience research that benefits one condition or disorder in fact has broad potential applicability for many conditions. In my view, these truths make it critical to help the broad brain science community break down silos, and encourage more collaboration that crosses traditional scientific boundaries, areas of expertise, and advocacy priorities.

One of the most critical collaborations is across what has traditionally been thought of as two largely independent enterprises, basic science and clinical research. In fact, we must recognize that both endeavors are necessary components of a continuum that leads to translation. In my view, we must approach the future of neuroscience with a focus on "translational basic science." We must encourage and facilitate scientists and clinicians to work as a team to translate scientific knowledge and discoveries into specific personalized approaches to diagnosis, treatment and prevention of disease. As we move forward, our mission must be to seamlessly integrate clinical relevance into scientific research while ensuring that the system continues to encourage those

foundational research advances for which future applications have not yet, but surely will, be discovered.

There is no better example of the importance of practical scientific application and translation than our increased understanding of synaptic brain plasticity, which is, in essence, the brain's ability to modify neural connections to better cope with new circumstances. This capacity for change and adaptation is a fundamental property of the synapse. The synapse is the place where neurons "talk" to one another using electrical and chemical signals, which in turn produces brain function and behavior. The foundational understanding of synaptic plasticity emerged from basic science. Yet today, our knowledge that the brain can adapt to injury or disease and help rewire itself is having a revolutionary impact on our understanding of learning and memory, and many other topics of deep important clinical relevance. Harnessing synaptic plasticity through innovative therapeutics will be critically important for treatment of chronic pain, psychiatric disorders such as PTSD and depression, and neurological disorders like TBI, stroke, and epilepsy.

Conclusion

In closing, I stress that today we live on the forefront of an era of breathtaking potential to advance biological knowledge and human health. And we are all fortunate to have NIH, NSF, DoD, VA, and many other strong public and private neuroscience research entities contributing to the world's finest research enterprise and a strong economic engine for America. As the nation considers difficult decisions in the face of economic strain, prioritizing strong funding and encouraging collaboration across the neuroscience spectrum remains a critical and wise investment precisely because it contributes so much to our health and economic strength.

The tremendous investments we have made in basic scientific study are paying off and should be strengthened. The field of neuroscience holds unbounded potential for addressing the broad range of neurological and psychiatric illnesses that impact millions of Americans annually and more than a billion throughout the world. Our future success will depend in large measure on sustaining the strong investment in basic discovery as well as team-oriented collaborative approaches between the basic researcher charting a path for new discoveries and knowledge and the clinical-physician researcher translating those discoveries into new and better treatments and cures. Mr. Chairman, Ranking Member Jordan, and members of the subcommittee, I look forward to the road ahead in this exciting field and what our success stories will mean for the American people.

Thank you again for the opportunity to testify. I look forward to answering any questions that you might have.

Mr. KUCINICH. Thank you very much.

We have another series of votes. Mr. Kennedy and I have conferred and we are each going to take 3 minutes for questions or comments, and then we are going to adjourn this.

But I would just say that there will be followup questions that myself and others will submit to you, and we will ask for your thoughtful consideration on the questions members of the committee submit.

Mr. Kennedy, you are recognized for 3 minutes, and then I will wrap it up.

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

As we are speaking today, a Rhode Islander in Fort Hood committed suicide, as we were conducting this hearing. He is from Middletown, Rhode Island, in my district. He committed suicide and murdered his wife. He leaves behind two children, one six and one is two. Dr. Parker, Kit Parker, who could very well have served alongside of this Rhode Islander in his service as a Rhode Island Guard, pointed out most poignantly, these are combat deaths. And they are part of the enemy's strategy. Whether they are killed in action or they are killed over here because of their wounds of that action that they saw, it is a death as a result of this war. And if we don't take it as such, we are not going to approach it as such. Because we will think of it as something else, other than part of our war effort.

So the urgency that you gave us, Kit, in terms of fighting this fight as if it were fighting the enemy, because this is the enemy's fight that they are taking to us, we have to take it back to them. And that kind of call to action that you gave us, so poignant, so powerful, serves to act as a catalyst for all of the things that Dr. Potter was saying about the need for a national priority to be put on this, that is going to return the science in short order on the emergency level that it is demanded, because we are not turning it around fast enough.

So for everybody here, that open source need for sharing of science, because we are all in it together, and the need for us to do it fast and furious for the benefit of the people who will come to benefit from this, and to bring it to a national scale is so welcome. I thank you all for that. That image, Tim, of the valley of death, the valley of death in translational research, from moving that research in the lab to the bedside to benefit people, that is the valley of death. That is the word you used, it is a valley of death. Every day longer we leave these veterans in that valley, we are shirking our responsibility to go in and set them free.

Thank you for your comments. Dr. Potter, if you could keep submitting for us the kinds of regulatory science reform you think would be necessary at the FDA to give Dr. Hamburg her support along with what we ask the NIH and other directors to talk about, so that when they come up with something, we can move it right into practice. If you could just close by commenting a little bit about where that is just such a lacking part of our FDA. No offense to them, they need the support from us.

Mr. KUCINICH. What we will do is ask if you will respond in a letter on that.

Mr. MORRISON. Certainly.

Mr. KUCINICH. If I may, I am going to try to make sure that we can get to vote here.

I want to thank Pat Kennedy again for being instrumental in creating this hearing.

Dr. Morrison, can high levels of stress impair synaptic plasticity?

Mr. MORRISON. Absolutely. Well, let me qualify that. Absolutely in animal models, there is no question about it.

Mr. KUCINICH. Dr. Akil, you said something that I thought was, everything you said, all the witnesses, is very important. But you said our brains are modeled by the social environment. That parallels the studies of David Bohm, the quantum physicist, who said that the world is a hologram of the brain, which is a hologram of the world. He was really looking at the holonomic theories of Karl Pribram. They got together and addressed the issue of the brain in a more global way, which is what your testimony, I assume, is advocating. When you talk about the choreography of the brain, you are speaking of the brain in a much broader sense, instead of things that are site-specific, you are looking at the brain in terms of its vastness?

Dr. AKIL. Yes. I think the idea is that things are integrated both in space and in time in the brain. That is how new functions emerge that we cannot comprehend by looking too molecularly. And the brain is the place where nature and nurture meet. So the social environment is just as important as the genes that we are born with.

Mr. KUCINICH. The work, then, of let's say a Maslow becomes relevant?

Dr. AKIL. Right.

Mr. KUCINICH. The work of Carl Rogers becomes relevant.

Dr. AKIL. Exactly, yes.

Mr. KUCINICH. I would just like conclude by saying one other thing. That is, we have spent time talking about soldiers, and Dr. Parker, thank you for bringing this very specific study of the impact of war, the physical impact of war and the long-term impact of war. We also need to look at post-9/11 America, when you talk about the social environment, the brain being modeled by social environment. We have an America that has been filled with fear and violence, whether it is vicarious through the media. That has to have an effect, it just does. I would like that to be a subject of perhaps another hearing in which maybe we can ask some of you to come.

We have 2 minutes to vote, Representative Kennedy.

Thank you for your dedication. As Chair, I can promise you that our subcommittee is going to stay in touch with each and every one of you. I think the work that you are doing is important to the future of the world. Thank you.

[Whereupon, at 5:35 p.m., the subcommittee was adjourned.]

○