STATEMENT

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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

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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.

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