SENATE SPECIAL COMMITTEE ON AGING

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State of Play: Brain Injuries and Diseases of Aging

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Mr. Chairman and Members of the Committee:

Thank you for the opportunity to appear before you today to discuss the current state and future needs for improving the treatment and management of mild traumatic brain injury.

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BACKGROUND

According to the most recent statistical data from the Center for Disease Control and Prevention (CDC), approximately 1.6 to 3.8 million people experience a traumatic brain injury (TBI) in the United States each year alone, resulting in 52,000 deaths. TBI was the leading cause of combat deaths in both Operation Iraqi Freedom and Operation Enduring Freedom; estimates range from 15% to 25% of all injuries sustained in warfare during the previous century involved TBI. Of significant concern for this Committee, pediatric patients struggle more than any other age group to return to function after a brain injury. Most relevant to this hearing: over 50% of deaths associated with falling in the elderly are due to TBI. Although interest in severe TBI has long dominated research studies, we now know the number of TBIs of mild to moderate severity far outnumber those with severe injury. In fact, annually it is now known that more than 1.7 million people are treated and released from emergency departments. Recent evidence suggests that participation in sports involving contact and/or collisions may alter regional brain metabolic processes and increase the risk of catastrophic neurodegenerative diseases, including chronic traumatic encephalopathy (CTE) which has been linked to repetitive concussion brain injuries. Over 300,000 sports injuries a year have a brain injury component. When considering the burden of TBI on our healthcare system consider that in the US each year over 70 billion dollars are spent from lost work days to intensive care units.

HEALTH CONSEQUENCES OF CONCUSSION

Contact sports are synonymous with mild TBI (mTBI), which is also known as concussion. As the brain accelerates and subsequently decelerates inside the skull its sensitive processes are stretched and damaged. Additionally, bruising presents at sites where high speed impact occurs against the inner skull. Returning to play too soon after a concussion increases the risk of experiencing another more serious TBI that can be caused by less force. Not to mention, those athletes who have experienced more than two concussions are at higher risk for permanent to prolonged symptomology. Recent findings supported by the NIH have shown that repetitive concussions may lead to progressive decline in brain functions over the life span. It is becoming more evident that athletes who have sustained multiple concussions are at risk for clinical depression and subsequent suicidal ideation. These athletes also tend to have memory and attention impairment with delayed information processing speed. Some reports state that of all the people engaged in athletics 19% may suffer a concussion each year. Individuals who experience concussions have up to a 20% likelihood of developing Post-Concussion Syndrome (PCS). Unlike the concussed who return to normal within 2 weeks, patients with PCS have long term disability with prolonged symptoms including: chronic headaches, fatigue, sleep difficulties, personality changes, sensitivity to light or noise, dizziness when standing quickly, and decreases in short-term memory, problem solving and general academic functioning. Clearly, anyone who has sustained a concussion needs to be immediately evaluated and treated by a physician, and closely monitored thereafter. Also, the individual should visit and be evaluated by a neuropsychologist, a specialist who can best monitor the athlete's symptoms and immediately put appropriate treatments in to play.

MILD CONCUSSION DEFINED; CHALLENGES WITH DIAGNOSIS

A mild concussion, is characterized by a confused or disoriented state lasting less than 24 hours; loss of consciousness for up to thirty minutes; memory loss lasting less than 24 hours; and structural brain imaging (CT scan) that yields normal results. Concussions are notoriously difficult to diagnose and treat. Each injury may have a different constellation of findings, and such findings can often be very subtle in their presentation as well as intentionally masked by the patient. Current sideline tests have multiple limitations, including low sensitivity, environmental factors, ease of implementation and equipment restrictions. Furthermore, return to sports participation, work, and military duty criteria are based on symptomatic resolution and normalization of neurocognitive function. With the former, reliance on the patient's report is required, and patients will frequently do whatever it takes to get back to their prior activities, including the use of deception. With the latter, baseline testing is needed for comparison, and many individuals will attempt to "sandbag" their baseline in order to be able to more easily pass the test. This is to say, just as you would expect a young athlete or soldier to do what it takes to return to the field,

the elderly also tend to do what it takes to preserve independence.

Finally, many technologies used for concussion diagnosis and clinical assessment have different limitations; including technically difficult application, diagnosis-only (ie. inability to inform return-to-play decision making), poor sensitivity, and high costs.

A COMPOUNDING INJURY

As a compounding injury, a significant consequence of not properly treating mTBI is that suffering one injury makes a second more likely; and the second injury will most likely be worse than that first; and so on and so forth. Chronic traumatic encephalopathy (CTE), a form of neurodegenerative disease, has been recently shown to be associated with repetitive concussions. CTE is characterized by a progressive taupathy, neuritic threads and neuronal TAR DNA-binding protein-43 (TDP-43) proteinopathy. Tau protein aggregation and formation of neurofibrillary tangles is also associated with the loss of control of mood, emotions, and intellectual functioning. The pathological hallmarks of CTE have been recently discovered in the brains of professional athletes who suffered repetitive TBI and in brain tissue from deceased combat veterans diagnosed with psychological disorders such as PTSD and manic depression. In fact, it is now widely recognized that the behavioral sequeale of CTE can mimic Alzheimers Disease (AD) and Frontotemporal Dementia (FTD), including memory loss and depression. The severity of AD has been associated with abnormal hyper-phosphorylated tau containing aggregates of TDP-43. Repetitive TBI with the development of CTE leads to abnormal TDP-43 expression in about 83% of cases. Thus, it is imperative to develop a therapeutic intervention which can block the cellular and molecular cascades following TBI that lead to tau misfolding and aggregates, NFT formation and tau proteinopathy. The recent elucidation that NFT is made of tau and amyloid fibers should make it possible to select specific drugs and molecules that may stop or prevent the process from progressing, rather than simply suppressing the symptoms. That is to say, simply, concussion may not have to be a compounding injury at all. The findings of tau and TDP-43 are not only linked to CTE but also to Anterior Lateral Sclerosis (ALS). ALS is a degeneration of the motor portions of the spinal cord that allow for voluntary muscle activity. Recently, autopsied victims of brain trauma also diagnosed with ALS have shown that these pathological markers are not only in the brain but have diffused into the spinal cord.

THE AGING VETERAN COMMUNITY

Commonly referred to as a signature wound of the last twelve years of sustained combat in Iraq and Afghanistan, TBI remains number one on the Combatant Command (COCOM) medical priority guides

because of the impact on readiness and combat effectiveness, as well as the long term effect on service members' health and quality of life. According to Defense Medical Surveillance System (DMSS), Defense and Veterans Brain Injury Center, of the total 253,330 *reported* traumatic brain injury (TBI) cases between January 1, 2000, and August 20, 2012, 194,561 have been mild. As with other populations, combat-related brain injuries can result in serious neurological and psychological disorders, such as memory impairment and suicidal ideation. Additionally, and perhaps unique to the military and veteran community, concussion can amplify PTSD behaviors. Given the seriousness of this injury on both military readiness and the aging veteran population, as well as the translation of any findings to the overall civilian population, the Department of Defense and Department of Veterans Affairs are collaborating on concussion research. The majority of their research funding and effort, however, has been spent on diagnosis and prevention, rather than treatment. Given the compounding nature of concussion, as well as the enormous cost of treating our already aging veteran population, in my professional opinion more emphasis must be placed on developing treatments. There are, however, bright spots. The Army's Medical Research Material Command (MRMC) is working to fund research on treatments; the Combat Casualty Care Directorate has a staff that is attuned to their mission of treating combat injuries and, when possible, returning soldiers to the battlefield. Dr. James Kelly, Executive Director of the National Intrepid Center of Excellence, is also leading the way in efforts to treat our Wounded Warriors. The work that both of these organizations are doing right now, I believe, will yield positive results that will translate to the civilian population just as other areas of military research have ultimately done so. Given the translational nature of this research, this Committee, the Committee on Veterans Affairs, the Armed Services Committee and the HELP Committee should continue to emphasize, across Committee jurisdictions, the importance of the effort to find a ***treatment*** for concussion.

KIDS AND CONCUSSION; THE UNKNOWNS

By midnight tonight, nearly thirty children in the U.S. will have died from head injuries incurred today and many more will develop lifelong disability from their TBI. Even more will exhibit at least transient impairment of learning, development, and behavior. Although head injury is the leading cause of death and disability in children, there are only general management guidelines, and no Class I evidence supporting any standard therapy. While only a modest number of pediatric clinical trials for traumatic brain injury (TBI) have been conducted, nearly all pediatric trials and over 100 adult TBI trials have failed to show significant neuroprotective benefits of any specific therapy. More attention to the potential risks associated with TBI in the developing brain is needed to develop proper management and treatment strategies. While we do not fully understand the vulnerability of a child exposed to repeated TBIs in

sports and household settings, we do recognize that this population struggles even more than the adult population to recover from a single TBI. Because the brain is not fully developed until people are in their early 20s, the risk for serious brain injury is greater for those athletes who are younger than 25. The risk may be particularly great for high school athletes because they are big and strong enough to hit each other with tremendous force, but their brains are certainly not mature. Therefore, dangers in the near and long term are clearly highest in a younger population of athletes.

BRAIN INJURY IN THE ELDERLY; DRAMATIC INCREASES WITH PROLONGED LIFE SPAN

In the opinion of the World Health Organization, TBI will surpass many diseases as the major cause of death and disability by the year 2020. Approximately 10 million people worldwide are affected by TBI per year. Often neglected, elderly TBI patients are going to be an increasing financial burden to the society as our population continues to age. The CDC has identified concussion as a silent epidemic and the elderly portion of this diagnosis the silent population. Falls are the leading cause of TBI in the elderly. Following a TBI an elderly person has much more trouble returning to normal. The aged brain is not equipped to recover from trauma like more youthful adult brains. Additionally, the elderly have a much harder time recovering when left non-ambulatory and from avoidance of other transmittable conditions associated with trauma as their immune system is weaker with age. Often following a TBI an elderly patient will be transferred directly to long term housing. Many of the elderly are on blood thinners for other conditions and therefore more likely to acquire a hematoma with increased intracranial pressure following a blow to the head. The CDC has made a strong effort to educate caregivers on how to reduce falls in the elderly however studies are still needed to determine specific treatment and management strategies for the elderly who have sustained a TBI which tends to present differently than in younger adults.

RESEARCH METHODS

Recent workshops of the TBI and stroke scientific communities have examined why agents with preclinical therapeutic efficacy have failed to translate to clinical success. In addition to challenges imposed by the heterogeneity of TBI and differences between rodents and humans, they concluded agents should be tested in multiple animal models, using clinically relevant outcomes, short-term and long-term endpoints, and histological and functional metrics. Because of marked differences in maturation, morphology, and injury mechanisms, current and popular rodent TBI preclinical therapy trials must be complemented by additional preclinical trials. Pig models are highly developed and currently should be considered the top choice. Research is needed to develop time-courses and mechanisms associated with focal and diffuse injuries that will identify time intervals and targets for future clinical care to develop

management and treatment strategies. Further research is needed to develop clinically relevant imaging and neurointensive care monitoring methods in animal models.

CONCLUSIONS

Concussions and other forms of TBI will no longer be a silent epidemic as we continue to shine light on the negative effects of the disorder. TBI transcends generations and populations from the infant to the elderly and from athletic fields to battlefields. In our fast-paced and too often violent world it is no surprise that head injuries are becoming all too common. The current cost to society to care for TBI patients is over 70 billion dollars per year in the US alone. From lost work for the victim as well as their family members to surgical procedures to reduce pressure on the brain, the consequences of TBI are catastrophic to so many involved. Research to date has focused on identifying the pathology of the injury and diagnosing based on individual presentation. Further funding has gone to prevention to try and improve protective gear and educate caregivers/coaches/commanders on removing risks. Unfortunately, no funding has focused on developing new treatments from a pharmaceutical or rehabilitation perspective. As many more parents are keeping their kids out of sports these days due to fear of concussion this may lead to other disorders such as obesity and juvenile diabetes as a result of lack of activity. Furthermore, no one wants to see rule changes to our favorite past times which reduce the excitement of the games. Even more disturbing for the safety of our country would be a reduction in armed forces enrollment.

In my professional opinion we are dealing with two major issues that need our complete focus and this focus requires research and development funding and collaboration. First, concussions are compounding. In other words, if you have one you are more likely to have two and they become additive when it comes to pathological findings and subsequent negative presentation. Therefore we need to develop new ***acute*** pharmaceutical treatments that are delivered immediately after the concussion to prevent the compounding nature of subsequent concussions. By developing new rehabilitative techniques they can be used as an adjunct to these drug treatments. Second, we have a population that currently has or is predisposed by multiple prior concussions to AD and ALS-like pathologies. Therefore we need to develop new ***chronic*** pharmaceutical treatments that can block the progression of these pathologies and stop the disease process in its path.

Prevacus, Incorporated is positioned today to develop a pharmaceutical for the ***acute*** treatment of concussion and prevent the compounding effects of brain trauma. Designed as a nasal inhalant the drug will be readily available in the field for use by athletic trainers, medics and ambulance technicians. The lead candidate is a neurosteroid and in toxicology studies. Clinical trials are designed to start in January,

2015 if sufficient funding is acquired. We have also designed 22 other neurosteroids and are poised to start preclinical studies with 2 of them this summer in animal models of AD and ALS. Now is the time for leaders in science, medicine and government to come together to advance new treatments for concussion and halt the progression of others who are already facing the TBI-associated pathology.