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State of Play: Brain Injuries and Diseases of Aging

Testimony before the

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Special Committee on Aging

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Mr. Chairman and Members of the Committee:

I am pleased to testify at today's hearing on brain injury and diseases of aging. I will present my perspective as a neurologist, scientist, and Deputy Director of the National Institute of Neurological Disorders and Stroke (NINDS) on what we know, where there is uncertainty, and how the NIH is working with other agencies, the private sector, the scientific community, and patients to address the gaps in our knowledge.

Traumatic Brain Injury (TBI)

I begin with a reminder that TBI is remarkably common, especially among the elderly. The U.S. Centers for Disease Control and Prevention (CDC) estimates that every year at least 2.5 million people in the United States suffer TBIs and more than 50,000 die[1]. As the CDC notes, this estimate does not include very large numbers of people who experience mild TBI but do not seek emergency care. Adults aged 65 years and older have the highest rates among all age groups of TBI-related hospitalization and death. Older people also recover more slowly and die more often from these injuries than do younger people. The most common cause of TBI in this age group is falling. This month, NIH and the Patient Centered Outcomes Research Institute (PCORI) announced a five year $30 million national study that will test a uniquely patient-centered approach to reducing rates of fall-related injuries among non-institutionalized older adults. The National Institute on Aging (NIA), which leads this study for the NIH, also supports research on age differences in TBI, as well as research on dementia.

[1] http://www.cdc.gov/traumaticbraininjury/get_the_facts.html

Although I will focus today on consequences of TBI that may not become apparent for decades after trauma, bear in mind that TBI can immediately affect many aspects of brain function. Problems with attention, memory, and thinking, especially "executive function," are common and persistent after moderate and severe TBI, as are social and emotional problems. Most people with mild TBI appear to recover completely, but perhaps ten percent report lingering problems months after injury, classified as the *post-concussive syndrome.* Why some people have persistent problems is an important, but poorly understood, public health issue. This May, at the White House "Healthy Kids and Safe Sports Concussion Summit," the National Collegiate Athletic Association (NCAA) and the Department of Defense (DOD) announced that they will jointly initiate the largest study to date of concussion and head impact exposure in sports to better understand the features that predict long term problems.

CHRONIC TRAUMATIC ENCEPHALOPATHY

Simply put, there is compelling evidence that repeated blows to the head can lead to a specific form of dementia. This phenomenon was recognized in boxers as early as the 1920's and was thus labeled *dementia pugilistica.* Now called *chronic traumatic encephalopathy,* or *CTE,* this disorder has been identified in the autopsied brains of athletes from other sports, including football, hockey, and soccer, and in brains from a few military veterans who were exposed to blast injury as well as other forms of TBI[2]. In addition to other signs of degeneration, including loss of brain cells in advanced disease, the brains of deceased people with CTE exhibit characteristic abnormal clusters of a protein called *tau* inside neurons. Tau aggregates are also one of the two key

[2] Brain 136:43-64 2013

findings in the brains of people with Alzheimer's disease, along with deposition of a protein called *amyloid* outside the cells. Multiple studies have demonstrated that tau is altered and amyloid precursor protein is increased after head injury in animals, and a recent human study using amyloid-PET (positron emission tomography) scans demonstrated transient increases in amyloid in the brain after moderate to severe head injury[3]. Amyloid-PET scans use small tracer doses of radioactive markers tailored to bind to amyloid to create an image of amyloid deposition in brain. Tau-PET scans, now in late stage development, will provide the ability to scan for tau deposits as well. The anticipated introduction of Tau-PET scanning could revolutionize the study of CTE by providing the ability to diagnose the condition during life. Abnormal tau deposition inside brain cells is the pathological signature of CTE and Alzheimer's and is also implicated in other forms of neurodegeneration, including frontotemporal dementia (FTD) in which mutations in the tau gene cause neurodegeneration. Surprisingly, recent evidence suggests that tau and other abnormally aggregating proteins can spread from cell to cell in the brain, which may represent a key insight leading to new strategies to treat Alzheimer's, CTE, Parkinson's, and other neurodegenerative diseases. Because CTE may be the purest form of an acquired neurodegeneration, studying CTE may provide clues on cell to cell tau propagation for other neurodegenerative disorders.

Although we know that repeated TBI can cause CTE, there is much we do not know about this disease. Perhaps the most critical roadblock is the lack of diagnostics that can definitively identify CTE in living people. Consequently, CTE can only be confirmed or refuted upon examination of the brain at autopsy. Without such a

[3] JAMA Neurology 71:23-31. 2014

diagnostic, we cannot estimate how frequently CTE occurs or how the number, timing between concussions, severity, and direction of blows to the head affect the likelihood of CTE. We do not know how age, gender, lifestyle, genetics, or other individual differences affect susceptibility. We do not have a good understanding of the clinical features that are specific for CTE, especially in the early stages. The latter is especially concerning given that varying degrees of tau pathology have been repeatedly found on brain examination in men without dementia who had a history of concussions and died from suicide. We do not know whether blast injury or repetitive TBI might lead to CTE in our exposed service members or whether it is connected to suicides in active military and veterans. Policy-makers must ensure that in all such cases brains be autopsied and carefully assessed for signs of CTE. Finally, we do not understand how trauma triggers later neurodegeneration, though altered tau due to injury, then propagation throughout the brain provides a tantalizing clue. Most importantly, no interventions are proven to prevent the occurrence of CTE.

NIH is actively addressing these gaps in our knowledge. In September 2012, the Foundation for NIH established the Sports and Health Research Program with a generous donation from the National Football League. Scientific workshops in December 2012 and July 2013 convened experts in CTE, Alzheimer's disease, and other dementias to discuss the best pathways forward. Based on that guidance, two large, cooperative projects, led by investigators at Boston University and at Mount Sinai Hospital in New York City, have been funded that will define the scope of long-term changes that occur in the brain years after a single TBI or after multiple concussions. Through these projects ten neuropathologists from eight universities are coordinating

research to describe the chronic effects of TBI in brain tissue from hundreds of individuals in order to develop standards for diagnosis and staging. The Mount Sinai team will examine brain tissue for signs of CTE from elderly participants of the NIA-funded Adult Changes in Thought study who had a history of TBI at some time prior to death. Both teams will examine brain tissues collected by the NIH Neurobiobank from individuals who died years after a variety of TBI exposures. These studies will provide a foundation for understanding how commonly CTE occurs and, more generally, whether TBI contributes to development of dementia.

In these two CTE cooperative projects, neuropathologists will work with advanced brain imaging teams to identify a signature of CTE on brain scans that will allow clinicians to diagnose CTE in living individuals. The second major effort of the Sports Health Research Program will be a longitudinal study that will define the clinical characteristics of CTE over time and evaluate advanced neuroimaging techniques to detect changes in brain structure and function, including use of tau-PET imaging to diagnose and monitor progression of CTE. NIH also supports research to develop brain imaging that can detect mild TBI and post concussive syndrome, which are usually not evident in conventional brain scans. For example, *diffusion tensor imaging* is a variant of the more familiar MRI (magnetic resonance imaging) that better tracks nerve fiber pathways. This method has shown promise for studying the relationship between head impact exposure and cognition in college athletes over a single season, and joint NIH-DOD research using this technique has also identified brain damage in soldiers diagnosed with mild TBI whose conventional brain scans appeared normal.[4] Ongoing studies are also developing behavioral and laboratory tests that can be used on the

[4] Neurology 82:1-7 2014; New England Journal of Medicine 364:2091-100, 2011

sidelines to detect concussions or help determine in the days following when an athlete is ready to return to play.

TBI and DEMENTIA

In addition to CTE from frequent brain trauma, there are compelling reasons to investigate whether multiple TBIs, or even a single TBI, increase the likelihood that a person will develop Alzheimer's disease or other types of dementia. TBI, especially moderate and severe, can certainly cause immediate, long lasting cognitive problems. This may affect persons' "cognitive reserve" and would diminish their ability to compensate for brain changes due to aging or neurodegeneration, increasing the likelihood that functional problems become apparent. In addition, the underlying mechanisms of damage to the brain from TBI and from neurodegenerative disorders are closely intertwined. Chronic inflammation, as well as tau and amyloid changes, are associated with both conditions, raising the concern that changes due to TBI might accelerate age-related neurodegeneration such as Alzheimer's disease. Some large epidemiological studies have found an association between later dementia and a prior history of TBI, especially moderate and severe TBI. This includes, for example, a prospective study of World War II veterans and a recent very large nationwide population study in Taiwan[5]. However, other large epidemiological studies have not found an association, especially for mild TBI[6]. It is also unclear whether the TBI associated dementias that are detected in these studies arise from Alzheimer's disease, CTE, or other types of dementia.

[5] Neurology 55:1158-66 2000; PLOS ONE 8:e62422

[6] Neurology 53:1959-62 1999; J Neurology Neurosurgical Psychiatry 84:177-82 2013; reviews in J. Alzheimer's Disease & Parkinsonism 4:137 2014 & Lancet Neurology 11:1103-12 2012

Research is continuing to address these questions. In addition to the studies already described on long term consequences of TBI, an NIH supported study is following a cohort of former NFL football players to determine, among other questions, whether genes affect susceptibility to later problems. The DOD is funding a parallel study to the Alzheimer's Disease Neuroimaging Initiative (ADNI) to investigate the link between TBI and subsequent dementia among Vietnam war veterans who suffered TBI, using the same scientists and protocols as the main ADNI project, which is jointly funded by NIH and private sources through the Foundation for NIH. The DOD also launched a new Chronic Effects of Neurotrauma Consortium to investigate potential links between TBI in the military and cognitive decline in veterans.

More generally, researchers are increasingly attending to overlap among causes of dementia, whether TBI and Alzheimer's, Alzheimer's and vascular dementia, or neurodegeneration from other causes. We now know, for example, that there is a spectrum from Alzheimer's disease to vascular dementia, the second most common dementia, which is due to abnormalities in brain blood vessels. Most patients have neither isolated Alzheimer's nor pure vascular dementia, but rather contributions from both. There is also suggestive evidence that TBI may contribute to other neurodegenerative disorders, including FTD, amyotrophic lateral sclerosis (Lou Gehrig's Disease) and Parkinson's disease. The 2012 NINDS Stroke Research Priorities Meeting and the 2013 Conference on Alzheimer's Disease Related Dementias both stressed the importance of understanding the overlap among types of dementia. The latter meeting was part of National Alzheimer's Project Act (NAPA) activities, and

the NAPA Council has incorporated those recommendations into the National Alzheimer's Plan.

DEVELOPING TBI INTERVENTIONS

NIH supports research to develop interventions that prevent immediate and delayed problems from TBI, from laboratory studies in animals through large, multi-site clinical trials. NIH research has contributed to better critical care that has dramatically improved survival from severe TBI. NINDS and partners in Europe and Canada recently launched the International TBI Research Initiative. This prospective, observational study of 3,000 adults and children with TBI in the United States, coordinated with large studies by the European Union and the Canadian Institute of Health Research, will inform TBI classification and identify those therapies associated with the best outcome. NIH laid the foundation for meaningful comparison across these and other future studies by working with the research community and other federal agencies through the NINDS Common Data Elements program to harmonize the data that are collected and the way data are categorized. The DOD and NIH-led Federal Interagency TBI Informatics System (FITBIR) provides a database for sharing information from these and other TBI studies among qualified investigators.

BASIC RESEARCH

Progress in basic neuroscience has yielded advances in understanding the biology of the brain in health and disease, and an impressive array of tools to study the brain that will drive progress against TBI, dementia, and other brain disorders. The Human Connectome Project, for example, is applying advances in computer science, math, and diffusion tensor MRI brain imaging to develop a complete picture of the brain's

functional architecture in more than 1000 people, that is, a map of how different brain areas are connected and work together in the living brain. Pathologic studies demonstrate that damage, called "shear injury," in the brain's connections or "white matter" is common in moderate and severe TBI. Shear injury, which may occur diffusely throughout the brain, is relatively invisible with conventional imaging techniques. The Connectome will greatly enhance the ability to recognize and quantify the disruption in communication pathways between brain regions, and why some people's brains compensate better than others. Complementing this project at a more fine grained level of analysis, the President's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is developing tools with the spatial and temporal resolution to yield a dynamic, real time picture of how circuits formed by millions of interconnected nerve cells and synapses work. The BRAIN Initiative may ultimately yield insights about how TBI, Alzheimer's, and other disorders affect the functioning of important brain circuits and how the brain attempts to recover or compensate for these changes.

This January an NINDS intramural research team showed the power of applying emerging methods from basic neuroscience to TBI[7]. These researchers developed a novel mouse model of mild TBI and used advanced microscopy and cell labeling techniques to watch in real time in living animals how particular types of cells responded to mild TBI from the start. The investigators saw the swarming of immune cells and leakage of dye out of blood vessels on the surface of the brain during the initial inflammatory response and the recruitment of brain supporting cells that

[7] Nature 505:223-228 2014

reconstituted damaged protective barriers. Using MRI brain imaging, the team was also able to detect similar dye leakage from surface blood vessels in humans after concussion, underlining the likely relevance of the animal studies. Because researchers could watch the cells' responses to pharmacological agents, they could analyze how chemical signals orchestrate damage and repair responses and test potential interventions that target these mechanisms. Methods like these promise to greatly increase our understanding of how the brain reacts to TBI and why there may be long term consequences.

CONCLUDING REMARKS

To answer the key challenges discussed today, NIH supports a full spectrum of research and works closely with others, including the DOD and the international scientific community. With great anticipation we await the introduction of new MRI and PET brain imaging methods that will enable us to identify and quantify important brain changes in living TBI survivors for the first time. Longitudinal studies can then determine what occurs in the brain that leads to delayed cognitive decline, and whether Alzheimer's disease is more likely to occur. New structural and molecular imaging techniques may also enable scientists to identify and track markers of the neurodegenerative process over time, which can provide targets against which to test new therapies. Progress is imperative because of the enormous impact of TBI and dementia on individuals and their families, on the public health, and on the economy of the United States and the world. Thank you.

Department of Health and Human Services

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Walter J. Koroshetz, M.D.

Walter J. Koroshetz, M.D. has been Deputy Director of the National Institute of Neurological Disorders and Stroke (NINDS) since January 2007. Among his many activities within NINDS and across the NIH, Dr. Koroshetz is a member of the Trans-NIH Emergency Medicine Task Force. Prior to his appointment at the NINDS, Dr. Koroshetz was vice chair of the neurology service and director of stroke and neurointensive care services at Massachusetts General Hospital (MGH). He was also a professor of neurology at Harvard Medical School and has led neurology resident training at MGH since 1990.

Before coming to the NINDS, Dr. Koroshetz had been on NINDS intramural review and oversight committees, been involved in various NINDS symposia and clinical trials, and served as the Institute's representative to the American Neurological Association's Career Development Symposium. He was a member of the NINDS-chaired Brain Attack Coalition (BAC), a group of professional, voluntary and governmental entities dedicated to reducing the occurrence, disabilities, and death associated with stroke. He led the BAC committee whose work resulted in significantly higher hospital reimbursement for acute ischemic stroke management. As an extramural grantee Dr. Koroshetz received NINDS funding for laboratory and clinical research projects on Huntington's disease, neuroprotection, and translational research in acute stroke.

He is a member of numerous professional societies, including the American Academy of Neurology, American Neurological Association, Society for Neuroscience, Huntington's Disease Society, American Society of Neuroimaging, American Stroke Association, and the National Stroke Association. He is associate editor for MRI with the Journal of Neuroimaging and was an associate editor of Cerebrovascular Diseases.

Dr. Koroshetz was born in Brooklyn, New York. He graduated from Georgetown University and received his medical degree from the University of Chicago. He trained in internal medicine at the University of Chicago and Massachusetts General Hospital. Dr. Koroshetz trained in neurology at MGH, after which he did post-doctoral studies in cellular neurophysiology at MGH and the Harvard neurobiology department. He joined the neurology staff, first in the Huntington's Disease unit and then in the stroke and neurointensive care service. During his career Dr. Koroshetz has conducted basic electrophysiology research in cell membranes and in cultures of nerve cells and glial cells (which support nerve cells). His clinical research has focused on finding new treatments for patients with Huntington's disease and stroke. He is the author of more than 100 peer reviewed publications as well as numerous chapters and reviews. He has supervised the training of more than 150 residents and fellows.