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

Statement of
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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.

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[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

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[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.

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[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.

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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 National Institutes of Health (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), Boston, Massachusetts. 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 magnetic resonance imaging (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 MGH. Dr. Koroshetz also 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.