



Testimony
Before the Subcommittee on Oversight and
Investigations
Committee on Veterans Affairs
United States House of Representatives

**RESEARCH ON ALZHEIMER'S DISEASE,
PARKINSON'S DISEASE AND DIABETES AT THE
NATIONAL INSTITUTES OF HEALTH**

Statement of

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Chairman Buyer and Members of the Subcommittee:

Thank you for inviting me here today to discuss three devastating diseases that disproportionately affect older Americans: Alzheimer's disease (AD), Parkinson's disease (PD), and diabetes. I am Dr. Judith Salerno, Deputy Director of the National Institute on Aging (NIA). Since the NIA is the lead Federal agency for AD research, I will be discussing a number of recent advances and ongoing activities in this area. With me to discuss the status of AD research is Dr. Marcelle Morrison-Bogorad, Director of the NIA's Neuroscience and Neuropsychology of Aging Program. I will also discuss ongoing Parkinson's disease and diabetes research at the National Institutes of Health (NIH). Dr. Diane Murphy, Program Director for Neurodegeneration at the National Institute of Neurological Disorders and Stroke (NINDS) and Dr. Judith Fradkin, Director, Division of Diabetes, Endocrinology and Metabolic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are also here today to answer any questions you may have about these research areas.

According to the U.S. Bureau of the Census, there are currently 26.4 million veterans of the armed forces in the United States, 37 percent of whom are over age 65, compared to 13 percent of the total U.S. population. The Veterans' Health Administration estimates that the number of "oldest old" veterans – those age 85 or older – will peak in 2012 at 1.4 million, representing an increase of 167 percent over 2000 levels. As with the general population, these older individuals are vulnerable to diseases and conditions of aging, including AD, PD, and diabetes. The magnitude of the older veteran population, however, gives particular urgency to issues related to the prevention and treatment of such age-associated conditions for those who care for our veterans.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that starts slowly with a mild loss of memory but progresses relentlessly until it destroys one's ability to carry out even the simplest tasks. Causing this mental decline is an inexorable buildup of brain changes – insoluble deposits called plaques and tangles that accumulate in particular brain regions, damage from inflammation and oxidative stress, loss of connections

between nerve cells in memory and other pathways, and eventual death of these brain cells. AD's impact on individuals, families, the health care system, and society as a whole is profound: Approximately 4.5 million Americans currently have AD, with annual costs for the disease estimated to exceed \$100 billion.¹ Moreover, the rapid aging of the American population threatens to increase this burden significantly in the coming decades. Demographic studies suggest that if current trends hold, the annual number of incident cases of AD will begin to sharply increase around the year 2030, when all the baby boomers (born between 1946 and 1964) will be over age 65. By the year 2050, the number of Americans with AD could rise to some 13.2 million, an almost three-fold increase.²

But these numbers, however stark, do not tell the whole story. Although AD remains a major public health issue for the United States, we have made, and are continuing to make, dramatic gains in our ability to understand and diagnose AD that offer us the hope of preventing and treating the disease. Our efforts against AD have been greatly enhanced through the involvement of veterans and the research scientists of the Veterans Health Administration. For example, many NIH-supported Alzheimer's researchers hold VA appointments, and veterans themselves participate in a number of AD research studies. In addition, many of the major advances in understanding AD have come from work at the 29 NIA-supported Alzheimer's Disease Centers (ADCs) across the country, at which multidisciplinary research teams focus on the disease. Several of the ADCs are located at VA medical centers, including major programs in the Bronx, New York; Bedford, Massachusetts; Puget Sound, Washington; and Palo Alto and Martinez, California. Other ADCs, while not directly affiliated, have close ties with local VA centers – for example, collaborating on research projects or recruiting veterans for participation in clinical studies. Partnerships with VA researchers have strengthened our search for ways to delay and, ultimately, to prevent the devastation of this disease.

¹ Data from the Alzheimer's Association. See also Ernst, RL; Hay, JW. "The U.S. Economic and Social Costs of Alzheimer's Disease Revisited." *American Journal of Public Health* 1994; 84(8): 1261 – 1264. This study cites figures based on 1991 data, which were updated in the journal's press release to 1994 figures.

² Hebert, LE; Scherr, PA; Bienias, JL; Bennett, DA; Evans, DA. "Alzheimer Disease in the U.S. Population: Prevalence Estimates Using the 2000 Census." *Archives of Neurology* August 2003; 60 (8): 1119 – 1122.

Risk Factors

The risk of AD increases dramatically with age, with nearly half of all individuals over age 85 being affected.³ Many older Americans struggle with mild cognitive impairment (MCI), a condition that is frequently a precursor to AD; in one recent population-based study of cognition in the elderly, 22 percent of participants over 75, and 29 percent of those over 85, were diagnosed with MCI.⁴ Determining who is at high risk of developing AD and who is not – and why -- will enable us to identify potential targets for preventive intervention, as well as those individuals who might benefit most from such interventions.

Through laboratory, clinical and population-based research, we have identified a number of risk factors for AD, including both genetic and lifestyle factors. We already know three major gene mutations on Chromosomes 21, 14, and 1 are associated with early-onset disease – one of which was identified by a VA investigator, with NIA and VA support. Another gene, ApoE4, has been identified as a major risk factor for the more common late-onset disease. Recent findings are enabling us to close in on several others, thought to be on chromosomes 9, 10, and 12. The NIA's AD Genetics Initiative, the goal of which is to develop strategies for rapidly identifying the additional late-onset AD (LOAD) risk factor genes, associated environmental factors, and the interactions of genes and the environment, has already enrolled over 200 families or approximately 600 participants in its first year.

Recently, neuroscientists have become increasingly interested in a specific set of genes that may influence not whether, but when, a person might develop symptoms of neurodegenerative disease. Delaying the onset of AD symptoms by even five years could greatly reduce the numbers of people who will have the disease, as well as providing additional cognitively-healthy time to those who will eventually be diagnosed.

Recently, NIH-supported investigators found a gene on chromosome 10 that they believe influences the age of onset of both Alzheimer's disease and Parkinson's disease.

³ Data from the Alzheimer's Association. See also Evans, DA; Funkenstein, HH; Albert, MS; et al. "Prevalence of Alzheimer's Disease in a Community Population of Older Persons: Higher than Previously Reported." *JAMA* 1989; 262(18): 2552 – 2556.

⁴ Lopez O, Jagust WJ, DeKosky ST, Becker JT, et al. "Prevalence and Classification of Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study." *Arch Neuro* 60: 1385-1389, 2003.

Using a novel method to match the genes of people affected with these diseases with the age at which study participants started developing symptoms, the scientists found that one gene, GSTO1, was significantly associated with late onset of both Alzheimer's and Parkinson's. This important work gives us new clues to the role of genetics in the timing of late-life forms of these devastating neurodegenerative diseases.

Not only genetic but also lifestyle factors may influence risk of AD. For example, epidemiological studies, including one undertaken by NIA's intramural program involving veterans with head injuries sustained while on active duty during World War II, suggest that head injury may be a long-term risk factor. Other conditions such as heart disease, high blood pressure, and stroke may also increase risk. We are currently supporting several studies to determine whether treating these conditions will delay the onset of AD.

Type 2 diabetes is another potential risk factor for cognitive decline and AD. In a recent study, researchers found that compared to older non-diabetic women, older women with type 2 diabetes were about 30 percent more likely to score poorly on tests of cognitive function, and the risk increased with the duration of their condition. However, the diabetic women in the study who took glucose-lowering pills had a risk similar to non-diabetic women. Recognizing the potential link between type 2 diabetes and cognitive decline, NIH-supported researchers with funding from NIA and NIDDK are currently participating in an offshoot of the National Heart, Lung, and Blood Institute's Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. ACCORD evaluates whether more intensive glucose, blood pressure and lipid management can reduce cardiovascular disease in people with diabetes; the aim of this sub-study, ACCORD-MIND, is to test whether the rate of cognitive decline and structural brain change in people with diabetes who are treated with standard care guidelines is different than in people with diabetes treated with intensive care guidelines. We anticipate that 2800 people will participate in ACCORD-MIND.

Imaging

Powerful imaging techniques, including positron emission tomography (PET) and magnetic resonance imaging (MRI), are opening a window into the living brain, allowing us to visualize not only anatomical structures but also functional processes and activities

at the molecular level. The refinement of these techniques continues to have a profound effect on all areas of neuroscientific research. In fact, improvements in brain imaging, coupled with the development of more sensitive cognitive tests, are enabling us to diagnose AD in the research setting with greater precision than ever before. While there remains no scientifically validated method to visualize AD's pathological hallmarks - amyloid plaques and neurofibrillary tangles - in a living human, researchers have recently developed the first radiotracers, including a molecule called Pittsburgh Compound-B, that facilitate visualization of amyloid deposition in living AD patients using PET scans. Although further research is needed, these molecules may eventually offer us a powerful and accurate tool for the early diagnosis of the disease.

Advances in imaging also have the potential to enable us to visualize the effects of therapeutic interventions more rapidly and accurately, with the potential for making AD clinical intervention trials smaller, faster and more affordable. Finding a biological way to accurately track AD development and progression is one of the objectives of the NIA's Neuroimaging Initiative, a large-scale partnership among NIA/NIH, academic investigators, the pharmaceutical and imaging equipment industries, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the NIH Foundation, with participation from the Alzheimer's Association and the Institute for the Study of Aging. This initiative is slated to begin this year.

Prevention and Treatment

NIA is currently supporting 25 AD clinical trials, including large-scale prevention trials, which are testing agents such as hormones, anti-inflammatory drugs, statins, homocysteine-lowering vitamins, and anti-oxidants for their effects on slowing progress of the disease, delaying AD's onset, or preventing the disease altogether. Other intervention trials are assessing the effects of various compounds on the behavioral symptoms (agitation, aggression, and sleep disorders) of people with AD. As imaging and laboratory studies reveal more about AD's pathology, we are identifying a number of novel molecular characteristics that may prove to be targets for future treatment of the disease.

Disseminating information about prevention and treatment of AD, as well as general information about the disease, is the mission of the NIA's Alzheimer's Disease Education and Referral Center (ADEAR). Serving AD patients and their families, health professionals, and the general public alike, ADEAR staff answer questions about the disease, provide free publications, and offer referrals to local supportive services and AD Centers specializing in diagnosis and treatment. In 2003, ADEAR distributed over 675,000 free publications, and there were over 1.5 million unique visitors to the ADEAR website (<http://www.alzheimers.org/>).

Caregiving

Most of the over 4 million Americans with AD today are cared for outside the institutional setting by an adult child or in-law, a spouse, another relative, or a friend. Caregiving issues are of great importance, since perhaps one of the greatest costs of AD is the physical and emotional toll on caregivers. Our major clinical trial on effective caregiver interventions, Resources for Enhancing Alzheimer's Caregiver Health (REACH), is funded jointly by the NIA and the National Institute of Nursing Research. One of the REACH sites is located at the Veterans Affairs Palo Alto Health Care System, a leading center in aging research. Now in its follow-up phase, REACH II, the study uses a multi-component intervention comprising the most effective interventions identified in REACH I. The intervention targets five areas – safety, self-care, social support, emotional well-being, and patient problem behaviors – and holds promise for alleviating the enormous burden of caregivers of Alzheimer's victims.

Parkinson's Disease

Background and Planning Efforts

Like AD, Parkinson's disease (PD) is also a devastating and debilitating neurological disorder; however, it is caused by the progressive loss of nerve cells that control movement. These cells produce the neurotransmitter dopamine, and their loss leads to tremors, rigidity, and slowing of movement. Other disabling symptoms can also occur, including speech problems and, in some individuals, difficulties with thinking, sleep, and depression. PD affects more than 500,000 Americans at any given time, and

its severity varies from person to person. We are fortunate that most patients can be treated successfully with the drug L-dopa, one of the most effective treatments available for any neurological disorder. However, many people become severely disabled, either when L-dopa loses its effectiveness or when increasing doses lead to debilitating side effects. The costs of this treatment and disability are believed to reach \$6 billion⁵ annually in the United States, making both treatment and prevention high research priorities. Though PD is diagnosed in some people younger than 50, it remains primarily a disease of aging, and for this reason, will continue to be an important health consideration for our veterans.

For more than three decades, the National Institute of Neurological Disorders and Stroke (NINDS) has been active in PD research, supporting early studies of L-dopa, fundamental research on the brain circuitry affected by PD, the development of critical animal models, and important advances in understanding the genetic basis of parkinsonism. In recent years, advances in areas of basic neuroscience, such as genetics, stem cells, natural growth factors, and brain circuits, have opened new opportunities to understand what causes PD and to develop improved treatments even for people with advanced disease. To exploit these opportunities, and ensure that public health needs are addressed, NINDS has led a large planning effort in PD research for the past four years, on behalf of the NIH.

The core of the NIH PD planning effort is the Parkinson's Disease Research Agenda, a five-year plan developed in March 2000 that provides a comprehensive overview of the research needed to understand the causes of PD and move forward with the development of treatments. NIH was already active in all of these research areas when the Agenda was created, and the Agenda identified several emerging opportunities for the NIH to pursue with greater emphasis.

The second phase of these planning efforts was initiated in July 2002, when NIH Director Elias Zerhouni convened a "Summit" with a small group of outstanding scientists to gain a better sense of where the field of PD research stood at the global level,

⁵ DHHS/NIH Disease-specific Estimates of Direct and Indirect Costs of Illness and NIH Support Report, FY2000 Update, citing Lierman, T.L., *Building a Healthy America*, 1992, 2nd ed., (Mary Ann Liebert, Inc.)

and to identify potential impediments to progress. The NIH developed the recommendations from the Summit into a matrix that outlined short-to-long range and low-to-high risk goals that address these roadblocks; a number of the short-term goals have been met already.

One of the core features of the 2002 PD Summit is the development of goals in the context of the research that is being supported by other Federal partners and private funding organizations. NINDS is currently tracking the NIH portfolio of PD research, along with the grants funded by the VA, the Department of Defense (DoD), and private foundations; today, staff monitor more than 1000 PD research projects. Through these analyses, regular discussions with VA and DoD staff, and meetings of the Federal-wide PD Coordinating Committee, NINDS and many other NIH Institutes continue to explore ways to facilitate collaboration.

Program Highlights and VA Collaborations

The clinical testing of promising treatments for PD remains a high priority. To address this, the NINDS developed the PD Neuroprotection Trial, or NET-PD, which will expedite the selection and testing of drugs that might slow or stop the progression of PD. In most clinical trials funded by the NINDS, investigators select the drugs and design the trial. By contrast, for NET-PD, NINDS first solicited suggestions for promising drug candidates from academia, industry, and voluntary health organizations, both here and abroad. Then, a team of clinicians, pharmacologists, and clinical trial experts, including NINDS scientific staff, evaluated the 59 compounds that were nominated. While the drug selection process was underway, the NINDS created a network of 42 (now 51) clinical sites around the country, including one that will recruit subjects at the Ann Arbor VA Medical Center; set up independent coordination and statistical centers; and designed the early phase clinical trials. The trial sites have already completed recruitment of people with early, untreated PD to participate in phase II clinical trials of the first two drugs selected by this process. Enrollment for trials of the next two agents is underway.

Surgical therapies for PD are also promising, particularly for individuals in advanced stages of the disease. To address this need, NINDS and the VA initiated the largest trial of deep brain stimulation (DBS) for PD to date in January 2002. DBS

involves the passage of electrical current through electrodes that are surgically implanted in very specific brain regions that are critical to motor control. The trial was designed to enroll over 300 subjects at multiple VA sites and affiliated academic institutions, and researchers will compare stimulation of two different brain regions to best practices in the medical management of Parkinson's. If DBS is shown to be the more effective approach, subjects on standard management will also receive DBS – and the effects of the two different stimulation strategies will be compared. The trial is progressing well, with over half of the needed participants recruited already, and the results are expected to have an important influence on the management of PD.

In addition to these two strategies, gene therapy may provide a third approach to treating PD, and NINDS is committed to moving as rapidly as is prudent toward human testing. In October 2000, the NINDS sponsored a scientific workshop on "Gene Therapy for Neurological Disorders." As a consequence of this meeting, several researchers formed a working group to address PD gene therapy in a concerted fashion and are conducting extensive development and testing of gene therapy strategies in animal models of PD. The NINDS oversight of this project uses milestone-driven funding, as is common in industry, and the first-year milestones were accomplished on schedule.

In the future, NINDS will continue to track the research in PD that the VA is supporting, and look for opportunities for collaboration wherever possible. The continued inclusion of the VA in efforts such as the PD Coordinating Committee will ensure that these efforts are productive for veterans and for all Americans.

Diabetes

Diabetes is a major – and escalating – public health problem in the United States. The sixth leading cause of death, diabetes lowers average life expectancy by up to 15 years. It is the leading cause of kidney failure, lower limb amputations, and adult-onset blindness, and adults with diabetes have heart disease death rates two to four times higher than those without diabetes.

Six percent of the population – some 18.2 million Americans – currently has diabetes; 90 to 95 percent of these people have type 2 (formerly called “adult onset”)

diabetes. About 1.3 million people are newly diagnosed with diabetes each year, the great majority of whom are 40 years of age or older. Disturbingly, nearly one-third of Americans with diabetes are unaware that they have the disease and are thus not taking the steps proven effective in reducing its complications. The estimated total financial cost for diabetes in the U.S., including costs of medical care, disability, and premature death, was \$132 billion in 2002, up from \$98 billion in 1997.⁶

Type 2 diabetes is associated with several risk factors, including older age and a family history of the disease. It is also strongly associated with obesity: more than 80 percent of people with type 2 diabetes are overweight or obese. Of Americans 60 and older, about 8.6 million, or 18.3 percent, have type 2 diabetes. Type 2 diabetes also occurs more frequently among certain racial and ethnic groups, including African Americans, Hispanic Americans, American Indians, and Native Hawaiians.

Preventing diabetes is the key to controlling the growing diabetes epidemic, and this is reflected in the NIH's program emphasis. For example, results of the recently completed Diabetes Prevention Program (DPP), a national clinical trial led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in collaboration with other NIH Institutes, demonstrated that individuals at substantial risk of developing type 2 diabetes could prevent or delay disease onset and improve their blood sugar levels through modest improvements in diet and exercise. This was the first major clinical trial to show that improvements in diet and exercise can be effective in reducing diabetes in a diverse population of at-risk people. NIH is conducting follow-up studies of the DPP participants to determine the durability of the DPP interventions, as well as studying the long-term effect of the interventions on the development of complications.

To promote translation of the DPP results into real health improvement for the American people, the NIDDK and the Centers for Disease Control and Prevention (CDC) recently developed the first national diabetes prevention campaign, "Small Steps. Big Rewards: Prevent Type 2 Diabetes." This program includes a toolkit for health care providers based on methods used in the DPP and a "game plan" for those with pre-

⁶ Statistics from the National Diabetes Information Clearinghouse, <http://diabetes.niddk.nih.gov/dm/pubs/statistics/>.

diabetes, with a calorie counter and tips on how to set goals, track progress, and start a walking program. The message is that by losing a modest amount of weight, getting 30 minutes of physical activity five days a week, and eating healthier, people with pre-diabetes can delay or prevent the onset of the disease.

The “Small Steps. Big Rewards” campaign is part of the larger NIDDK-CDC National Diabetes Education Program (NDEP). Another NDEP health awareness campaign, “Be Smart About Your Heart: Know the ABCs of Diabetes,” is aimed at helping people with diabetes and their health care providers to better understand the need to control all aspects of their diabetes to help prevent heart attacks or strokes. The NDEP is also participating in Health and Human Services Secretary Thompson’s “Diabetes Detection Initiative (DDI): Finding the Undiagnosed,” which is an effort to identify individuals at high risk for undiagnosed type 2 diabetes, and then refer them for initial screening in a clinical setting and follow-up care, if needed.

The NIDDK heads the Diabetes Mellitus Interagency Coordinating Committee (DMICC), which is charged with coordinating the diabetes research activities of all Federal programs, including the NIH and the VA, that are related to diabetes and its complications. Recent DMICC meeting topics have included leveraging the NIH investment in obesity research to enhance research and care for diabetes; jointly-funded (NIDDK/VA) research on the role of specialized footwear in preventing diabetic foot ulcers; and a new program called “MOVE” (Managing Overweight and Obesity among Veterans Everywhere), which was developed by the VA National Prevention Center with assistance from NIH scientists and is being piloted at 17 facilities.

The NIDDK and the VA also work together on the National Diabetes Quality Improvement Alliance, a collaboration of 13 private and public national organizations dedicated to the improvement of adult diabetes care.

In addition, the NIDDK supports studies of approaches to translate important advances from clinical trials in diabetes prevention and care into medical practice. Some approaches are targeted at improving care for specific populations, such as a low-income Latino population. Others study specific settings, such as a clinic serving inner city African Americans, or an interactive video conferencing system to connect health professionals at a large medical center with rural diabetes patients with limited access to

health care providers. The NIDDK and VA are collaborating on the CDC-led “Translating Research into Action for Diabetes” (TRIAD) study, which is examining the efficacy and cost-effectiveness of approaches to improve the quality of diabetes care, quality-of-life, and health status for people with diabetes in managed care settings. The VA has used the CDC TRIAD protocol to conduct a parallel study within VA sites that are geographically proximate to CDC TRIAD sites. Success in these trials could pave the way to widespread use of these interventions in communities throughout America.

Conclusion

As our population rapidly grows older, it is ever more urgent that we find effective ways to address diseases and conditions such as AD, PD, and diabetes that are associated with advanced age. Although we have made a number of important advances in the past few years, much work remains in each of these areas. By continuing and intensifying research, we can move forward in meeting the promise of a healthy old age by improving the health and well being of our veterans – and all Americans.