Senator Mikulski:

Thank you for inviting me to appear before you today to discuss Alzheimer's disease (AD), an issue of interest and concern to us all. I am Dr. Judith Salerno, Deputy Director of the National Institute on Aging (NIA), the lead federal agency for Alzheimer's disease research. As a geriatrician who has spent much of my career working with AD patients and their families, I am delighted to be here this morning to tell you about the exciting progress we are making toward understanding, treating, and preventing AD.

As you know, AD is a major public health issue for the United States, and it has a devastating impact on individuals, families, the health care system, and society as a whole. An estimated 4 million Americans are currently battling the disease, with annual costs estimated to exceed $100 billion. Moreover, the rapid aging of the American population threatens to increase this burden several-fold in the coming decades. However, despite the grim statistics, we have made, and are making, tremendous progress.

When I first began working with AD patients as a clinical researcher in NIA's Intramural Program in 1988, preventing or curing AD was considered, at best, a distant possibility. Our understanding of AD's underlying biology was limited, and for this reason it was difficult even to predict what might be effective as a treatment or preventive.

Today, the picture is considerably brighter. Through laboratory and population-based scientific studies, we have identified a number of risk factors for AD, including both genetic and possible lifestyle factors. Research supported by the NIA and the National Institute of Mental Health (NIMH) has identified several genes that can cause AD, thereby helping us identify pathways affecting its development or progression, which will lead to better molecular predictors of the disease even before it is clinically apparent. The development and refinement of powerful imaging techniques that target anatomical, molecular, and functional processes in the brain will give us an improved ability to diagnose AD early, while the patient can still take an active role in decision-making. These techniques, along with better neuropsychological tests, are also enabling us to identify people who are at very high risk of one day developing the disease and to determine just how the disease starts in brain. This knowledge, in turn, may allow early intervention in persons long before the disease affects their level of functioning.

Most importantly, we are making significant advances toward effectively treating, or even preventing, AD. NIA is currently supporting 18 AD clinical trials, seven of which are large-scale prevention trials. These trials are testing agents such as estrogen, anti-inflammatory drugs, and anti-oxidants for their effects on slowing progress of the disease, delaying AD's onset, or preventing it altogether. We eagerly await the results of these trials.

As we search for effective preventive interventions and treatments for AD, it is becoming clear that, rather than seeking only a "magic bullet" that will, by itself, prevent or cure the disease, we may be able to identify a number of potential interventions that can be used to reduce risk. Several recent studies have highlighted this.

For example, a recent study in the *New England Journal of Medicine*[1] indicates that elevated blood levels of the amino acid homocysteine, already considered a risk factor for cardiovascular disease, are associated with an increased risk of developing AD. The relationship between AD and homocysteine is of particular interest because blood levels of homocysteine can be reduced, for example, by increasing intake of folic acid (or folate) and vitamins B6 and B12. And, in fact, in a separate study in the *Journal of Neuroscience*[2], NIA researchers show that folic acid may protect mice against some of the symptoms of AD. NIA has ongoing clinical trials of these substances to test whether supplementation can slow the rate of decline in cognitively normal men and women as well as in women at increased risk for developing dementia, and a trial on people diagnosed with AD is due to start in 2003. Other studies have indicated that the use of statins, the most common type of cholesterol-lowering drugs, may lower the risk of developing AD. A study of statins to slow the rate of disease progression in AD patients is planned for fall 2002.

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[1] ***S. Sesdradri, A. Beiser, J. Selhub, et al., "Plasma Homocysteine As A Risk Factor For Dementia and Alzheimer's Disease," N Eng J Med*, 346:7, pp. 476-483.**

[2] ***I. Kruman, T.S. Kumaravel, A. Lohani, W. Pedersen, R.G. Cutler, Y. Kruman, N. Haughey, J. Lee, M. Evans, and M.P. Mattson, "Folic Acid Deficiency and Homocysteine Impair DNA Repair in Hippocampal Neurons and Sensitize Them To Amyloid Toxicity in Experimental Models of Alzheimer's Disease," Journal of Neuroscience*, 22:5, pp. 1752-1762.**

Another promising area of study is the role of mentally stimulating activities throughout life as a factor capable of maintaining cognitive health or even reducing the risk of cognitive decline or AD. Through its Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, NIA is currently exploring whether three specific interventions (on memory, reasoning, and speed of processing) can maintain or improve functioning in unimpaired, community-dwelling older adults. In addition, NIA-supported researchers recently found that more frequent participation in activities such as reading, doing crossword puzzles, or playing card games is associated with a reduced risk of later developing AD[3].

In addition, scientists funded by NIA and NIMH are developing and refining powerful imaging techniques that hold promise of earlier and more accurate diagnosis of AD, as well as improved identification of people who are at risk of developing the disease. For example, recent studies suggest that positron emission tomography (PET) scanning of metabolic changes in the brain and magnetic resonance imaging (MRI) scanning of structural brain changes may be useful tools for predicting future decline associated with AD and other neurodegenerative diseases. Researchers have also developed a new method of functional MRI (fMRI), a technique for visualizing activity of brain structures, that is both easier on the person being tested and capable of imaging smaller structures in the brain than has been possible in the past.

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[3] ***Wilson RS, Mendes de Leon CF, Barnes LL et al., "Participation in Cognitively Stimulating Activities***

These methodologies may also be useful for evaluating the efficacy of drugs in stemming the progression of AD or preventing its onset altogether. However, these and other emerging imaging techniques, while promising, require further testing and analysis before they can be routinely adopted in the clinical setting.

Another very important area of research involves easing the burden on caregivers of AD patients. In a sense, the AD "patient" is not only the person with the disease, but the entire family unit is. Most Americans with AD are cared for outside the institutional setting by an adult child or in-law, a spouse, another relative, or a friend. The financial costs of this care can be devastating to families; by one estimate, the average lifetime cost per person for patients with AD is $174,000. In addition to these financial burdens, caregivers frequently experience significant emotional stress and physical strain, yet they often do not receive adequate support.

NIA is investing in new approaches to assist these often forgotten Americans. A first priority is to assess the magnitude of the problem. For example, the ongoing Aging, Demographic, and Memory Study (ADAMS) has been designed to assess dementia and AD among Americans, the burden on caregivers, the economic cost of dementia to families and to society, and the burden of dementia over the course of the illness.

***and Risk of Incident Alzheimer Disease," JAMA* 287: 742-748.**

NIA is also supporting a study of a combined behavioral and drug intervention on patients with mild AD. In this study, caregivers will be key participants in the behavioral intervention, and the researchers hypothesize that this participation will reduce caregivers' psychological stress. In addition, NIA is supporting a large, multi-site clinical trial, REACH (Resources for Enhancing Alzheimer's Caregiver Health), to examine the effectiveness of various interventions to strengthen family members' capacity to care for individuals with AD. Thus far, the study has recruited over 1200 caregiver/care recipient pairs at six different sites across the country to participate in 12 different interventions. REACH is designed to show us what works to support caregivers and at what cost; we anticipate that the first findings from this trial may be available within the next several years. The NIMH is supporting a major project called the Clinical Anti-psychotic Trial of Intervention Effectiveness for Alzheimer's Disease (CATIE-AD) designed to help identify effective treatments for behavioral problems in AD, to help reduce the burden of care for both providers and families.

The process of translating basic science findings into clinical interventions is a challenging but critical component of AD research. One promising finding of recent basic research efforts was the ability of an immunization strategy to prevent or reverse formation of amyloid plaques in mouse models of AD. The initial clinical trial of this AD vaccine approach, conducted by the Irish pharmaceutical company Elan Corporation, plc and not an NIH-funded trial, was halted earlier this year

when a number of participants on the experimental treatment were found to have brain inflammation. Despite the unfortunate outcome of this trial, the science on which the study was based will provide a base on which to build better and safer strategies for arresting or reversing the brain lesions of AD. In collaboration with the National Institute of Neurological Disorders and Stroke (NINDS), NIA has already issued a Request for Applications (RFAs) and funded a number of studies to better understand the science underlying the vaccine approach.

The RFA with NINDS is one of many collaborations in which the NIA participates as part of its program of AD research. NIA frequently co-sponsors RFAs and Program Announcements (PAs) with other institutes, and leads an inter-institute AD working group. With NINDS and NIMH, NIA co-sponsors the Cognitive and Emotional Health Project (Healthy Brain Project), the goals of which are to assess the current state of knowledge of predictors of cognitive and emotional health with age and to accelerate the pace of scientific advances in these fields. NIA also collaborates with other Institutes, including NINDS and the National Institute of Child Health and Human Development, to conduct preclinical toxicology tests on compounds that may be effective against AD, and, with the National Center for Complementary and Alternative Medicine, co-sponsors a large clinical trial of ginkgo biloba as an AD preventive.

Fifteen years ago, we did not know any of the genes that could cause AD, and we had no idea of the biological pathways that were involved in the development of brain pathology. Now, we know the 3 major genes for early-onset disease and one of

the major risk factor genes for late-onset disease, and we have extensive knowledge of pathways leading to the development of AD's characteristic amyloid plaques in the brain. Ten years ago, we could not model the disease in animals. Today, transgenic mice are an invaluable resource for modeling amyloid plaque development in the brain and in testing possible therapies. Five years ago, we did not have any prevention trials funded and had no ways of identifying persons at high risk for the disease. Now, we have seven ongoing prevention trials, and scientists are identifying persons at high risk for developing AD by imaging, neuropsychological tests, and structured clinician interviews. And as recently as one year ago, we did not understand anything about how plaques and tangles relate to each other. Now, through the creation of the first double transgenic mouse to produce both plaques and tangles, we know that plaques in the brain can influence the development of tangles in brain regions susceptible in AD.

It is difficult to predict the pace of science or to know with certainty what the future will bring. However, the progress we have already made will help us speed the pace of discovery, unravel the mysteries of AD's pathology, and develop safe, effective preventions and treatments, to the benefit of older Americans.

Thank you, Senator Mikulski, for giving me this opportunity to share with you our progress on Alzheimer's disease. I would be happy to answer any questions you may have.