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BREAKTHROUGHS IN ALZHEIMER'S RESEARCH: NEWS YOU CAN USE

HEARING

BEFORE THE

SUBCOMMITTEE ON AGING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

ON

EXAMINING BREAKTHROUGHS IN ALZHEIMER'S DISEASE (AD) RESEARCH, FOCUSING ON RISK FACTORS FOR DEVELOPING AD, DEVELOPING SAFE, EFFECTIVE PREVENTIONS AND TREATMENTS FOR AD, AND "THE MAINTAIN YOUR BRAIN" CAMPAIGN

MAY 11, 2004

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C O N T E N T S

STATEMENTS

TUESDAY, MAY 11, 2004

ADDITIONAL MATERIAL

BREAKTHROUGHS IN ALZHEIMER'S RESEARCH: NEWS YOU CAN USE

TUESDAY, MAY 11, 2004

U.S. SENATE,
SUBCOMMITTEE ON AGING, OF THE COMMITTEE ON HEALTH,
EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:02 a.m., in room SD–430, Dirksen Senate Office Building, Hon. Kit Bond (chairman of the subcommittee) presiding.

Present: Senators Bond, Mikulski, and Dodd.

OPENING STATEMENT OF SENATOR BOND

Senator BOND. Good morning. The hearing of the Subcommittee on Aging of the Senate Committee on Health, Education, Labor, and Pensions will come to order.

Today we are here to discuss a very important and very difficult problem, that of Alzheimer's disease.

We welcome the distinguished panel and look forward to their sharing with us their views and possible rays of hope that they have for making progress on this very troubling disease.

It is a devastating disease with a deep impact on individuals, families, and our health care system, making this disease one of our country's greatest medical, social, and fiscal challenges.

Being parochial, I look at how it affects my State of Missouri, Senator Mikulski. In Missouri alone, there are over 108,000 people with Alzheimer's disease. Based on population growth, unless science finds a way to prevent or delay the onset of this disease, that number will increase to over 159,000 by 2025.

Today throughout the United States, approximately 4.5 million Americans have Alzheimer's, with annual costs in economic terms for this disease estimated to exceed $100 million. Based on current trends, by 2050, 11 to 16 million individuals could have this disease.

If these predictions become a reality, it could overwhelm our health care system and bankrupt Medicare and Medicaid. The numbers speak for themselves: Medicare costs for a person with Alzheimer's are almost three times greater than the average for all beneficiaries. And as the baby boomers age, the costs to the Medicare program will grow as well. The costs to Medicare will reach $50 billion in less than 10 years. The costs to Medicaid will increase 80 percent to $33 billion annually in less than 10 years.

And those are just the economic costs. The family costs and the human costs—those are the real tragedies. We have had the example of a former President who announced that he had Alzheimer's, and his wife has been a true champion in discussing very frankly the very tragic and difficult circumstances through which families go as a loved family member suffers and declines with Alzheimer's.

I know too many of them myself, whose wife or father or mother has suffered from Alzheimer's. I know my distinguished colleague has had great experience. And forget about the economic costs; the human costs, the lost touch with a loved one—I think Mrs. Reagan said that "He has gone to a place where he cannot be reached." That is the tragedy—that is the tragedy—that so many families confront today.

But over the past 20 years progress has been made in prevention, diagnosis and treatment of Alzheimer's. I understand that it is now possible to diagnose Alzheimer's with more than 90 percent accuracy. New drugs and new treatments are being introduced each year, and investments in research have set the stage for scientific and medical advances to prevent or slow the progression of this dreaded disease.

Alzheimer's research is producing some groundbreaking discoveries that offer hope for the 4.5 million people suffering from the disease today.

Today we are honored to have before the subcommittee a distinguished panel of doctors, researchers, and advocates to discuss Alzheimer's disease and the progress being made toward the understanding, diagnosis, treatment, and prevention of Alzheimer's disease.

I now turn to my distinguished colleague, the Senator from Maryland, Senator Mikulski, who has a deep and abiding interest as well as experience with Alzheimer's.

Senator Mikulski?

OPENING STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Thank you very much, Chairman Bond, for holding this hearing on breakthroughs in Alzheimer's research and also, for families dealing with this, essentially "news that they can use"—either things they can do to help their families, also to be able to give them hope, and also to explore ways where they are not going down efforts that will only lead to disappointment.

We are very pleased to have such a distinguished panel here of, as you said, leading research people, both research and clinicians, as well as the leading advocate organization, the American Alzheimer's organization, which has pursued both research and then ways for caregiving.

Today's hearing is going to focus on breakthroughs, providing information that will really tell us new facts and new ideas about breakthroughs in diagnosis, promising research pertaining to drugs and treatment, ideas on prevention techniques, and even research that might be going on internationally.

This topic is very near and dear to me for several reasons. My own father, a wonderful man, endured this himself, and Dr. Rabins' famous book, "The 36-Hour Day," was of such a big help

to my family and myself in really understanding what our father was dealing with and what we would have to deal with.

I am very pleased that the National Institute of Aging at NIH also has its primary site in Baltimore, at the Bayview Campus of Johns Hopkins, where leading geriatric research is going on. And, Senator Bond, when election years are not upon us and so on, you need to know that it is over there right nextdoor to a neighborhood that we call "Greek Town," so if you want to come and see leading-edge research and have a little heart-smart calamari, we will be happy to have you.

Senator BOND. That sounds like a deal. Is that before or after we have the crabs?

Senator MIKULSKI. We can just do it all day—but one of the things they are going to tell us is that the less you weigh at 70, the better your chances of not getting Alzheimer's.

We have made tremendous strides in improved diagnostic tools, helping providers to diagnose with 90 percent accuracy. This is really important, because when my Dad faced this in the mid-eighties, Alzheimer's was even becoming a catch-all for any form of memory loss, which was not good for the patient and not good for the family and, quite frankly, not good for the Medicaid system. So we are looking forward to hearing about those issues and the other issues related to medications that can alleviate the symptoms of Alzheimer's and also the increased knowledge of prevention.

This is why we are holding this hearing today, to hear from researchers and advocates as well as those involved in actual clinical work about these breakthroughs. Family caregiving for a family member with Alzheimer's faces these financial, physical, and emotional 36-hours days. I am fighting to make sure we help those families out, and in fact have introduced a $5,000 tax credit that if you have a family member with a chronic disease that requires medical management or supervision, you can get a $5,000 tax break for prescription drugs, specialized day care and specialized home care. I know it is another committee, but it is something to put out.

In terms of research, Senator Bond has talked about what it means in both Missouri and nationwide. We know that right now, 1.6 million Medicaid recipients are in nursing homes. About half of them, 800 million people, suffer from Alzheimer's. The impact on the families and the impact on the Medicaid budget is really severe. If we could have any type of breakthrough, for a cure or for prevention or even for cognitive stretch-out, every month that we can delay admission to a long-term care facility is important to the family and important to the taxpayer. Any month that we can delay would have those consequences.

If we can delay the onset or have cognitive stretch-out approaches and methodologies, I think it would be stunning. Everybody needs a cure, but even if we were able to keep people at home and keep memory and other functioning, it would be a great breakthrough.

So we are looking forward to hearing the testimony. We are very proud of the fact that our leadership worked from 1998, Senator Bond, when the National Institute of Aging budget was about $500 million, and working together with our appropriations—and we are

the appropriators as well on another committee—we increased it to $1 billion. This is very good—and it is not only Alzheimer's, and we want to hear from you, Dr. Hodes—we also have other legislation pending—the Alzheimer's Disease Research and Care Act of 2003, as well as looking at where we are going.

I will talk about where we are going after we have heard from our panel. But we are looking for promising research, and we are also looking for new approaches, like the chelation approach you talked about. And then also, we do know that there are other activities going on at NIH in the field of complementary medicine, and we look forward to getting some input from Dr. Straus.

But rather than me talking, we really want to hear from you. And I cannot thank you enough for what you are doing every day in your day-to-day work, whether it is heading up the NIH on research, whether it is heading up the advocacy organization, where they are being both clinicians and researchers, because you are truly making a difference. We welcome your enthusiasm and want to know how we can be on your side.

Thank you, Mr. Chairman.

Senator BOND. Senator, speaking about getting to the witnesses, we have the distinguished CVs of these four outstanding leaders, and we can either spend the day reading them or hear their testimony. And if you have no objection, I am going to introduce the full resumes of all of our speakers and just tell you very briefly about them.

The first witness will be Dr. Richard Hodes, Director of the National Institute of Aging, NIA, at NIH. NIA is the principal Federal funding agency for studies of the basic, clinical, epidemiological, and social aspects of aging. Dr. Hodes was named Director of NIA in 1993 but has enjoyed a long career in science at NIH as an investigator in the National Cancer Institute.

From the State of Missouri, we have Dr. John Morris, the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology at the Washington University School of Medicine, as well as professor of pathology and immunology and of physical therapy. He is director of the Alzheimer's Disease Research Center, Memory and Aging Project, and Memory Diagnostic Center at the School of Medicine and Barnes-Jewish Hospital, and also is director of the Center for Aging at Washington University.

Dr. Morris is the principal investigator for the program project, "Healthy Aging and Senile Dementia," and for the Alzheimer's Disease Research Center at Washington University, both funded by the NIA. He obtained a Leadership Award from the NIA for the Center on Aging.

I would like to turn over the next introduction to Senator Mikulski before introducing the final panelist.

Senator MIKULSKI. We also welcome Dr. Peter Rabins. He has been a member of the faculty of Hopkins since 1978. He is director of the Geriatric Psychiatric Program, and he has focused his career on psychiatric disorders of older persons.

In addition to this hands-on care as well as his research, he is the author of 180 articles, and his famous "The 36-Hour Day" book about what families and patients endure was first published in 1981 and is as current today as it was then in terms of the in-

sights. Also, in 1999, he published a book titled, "Practical Dementia."

But the committee should be aware that there is a newsletter that Hopkins puts out called "Health After 50." This is a newsletter for consumers to get the latest thinking on prevention, treatment, and so on, and his article, "Help for Early Alzheimer's" gave us a very good thumbnail sketch of some of the breakthroughs. So in addition to being members of the "genius club" at Hopkins, they actually can talk like regular people so we will know what they are saying.

Senator BOND. That will be very helpful.

Senator MIKULSKI. And we welcome him with enthusiasm.

Senator BOND. Our final witness that we are delighted to welcome today is Mr. Stephen McConnell, senior vice president for advocacy and public policy at the Alzheimer's Association.

Before joining the Association, he spent 7 years on the Hill as staff director of the Senate Special Committee on Aging under Chairman John Heinz and as a professional staff member for the U.S. House of Representatives Select Committee on Aging under the chairmanship of Representative Claude Pepper.

Mr. McConnell has been a teacher and has published in the fields of gerontology and social policy, and he holds a Ph.D. in sociology from the University of Southern California.

Gentlemen, we are delighted to welcome all of you, and with that, we will hear your statements. We have a timer up here set for 5 minutes, and we will take your full statements for the record, and we would like to go several rounds of questions.

So if you would please begin, Dr. Hodes, and we will take your full statement for the record.

STATEMENTS OF RICHARD J. HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD; JOHN C. MORRIS, M.D., FRIEDMAN DISTINGUISHED PROFESSOR OF NEUROLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS, MO; PETER V. RABINS, M.D., PROFESSOR, DEPARTMENT OF PSYCHIATRY, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD; AND STEPHEN McCONNELL, SENIOR VICE PRESIDENT FOR ADVOCACY AND PUBLIC POLICY, ALZHEIMER'S ASSOCIATION, WASHINGTON, DC

Dr. HODES. Thank you, Senator Bond and Senator Mikulski, for the opportunity to appear before you.

You have both very eloquently introduced the scope of the human and societal challenges posed by Alzheimer's disease, a topic of great interest and concern to us all.

In our quest to better understand the disease's starting point for learning how to deal with it, we search commonly for risk factors. The most telling risk factor for Alzheimer's disease currently understood is of course age, dramatically illustrated by the fact that nearly one-half of individuals age 85 and older are afflicted with the disease, and this, plus the projected increase in the number of older individuals in America, comprises the real urgency that you have introduced in your own comments.

Among the risk factors that have been identified are both genetic and environmental ones. We have identified three genes which are responsible for early onset Alzheimer's disease, and these have been invaluable in pointing to mechanisms, molecular and cellular, that provide new targets for interventions to come, in addition to identifying one major risk factor for late onset disease, the APOE gene.

We recently announced and I am happy to say have now implemented a new Genetics Initiative that is a collaboration among many of the Alzheimer's centers and investigators with the goal of identifying yet more genes involved as risk factors, again to the end of identifying new targets of intervention.

We are also greatly concerned with identifying modifiable risk factors. Among them are those that are cardiovascular risk factors as well. And one, to note a recent report, is diabetes. Diabetes, a disease which afflicts some 17 million Americans, has been shown to be associated with increased risk of loss of cognitive function and of Alzheimer's disease.

One recent study identified that in older women with Type 2 diabetes, the risk of Alzheimer's disease was increased, but that in women who were successful in controlling their blood sugar levels, in fact risk was reduced to the level of nondiabetics. In pursuit of this as a potential intervention, NIH is currently supporting a study, ACCORD, in which we will determine in a controlled clinical trial whether vigorous control of blood sugar will in fact be effective in preventing loss of cognitive function and the rate of development of Alzheimer's disease.

In addition to this search for risk factors, one of the modalities that has been particularly promising of late has been that of imaging. As was noted, we are now looking very seriously at ways in which we can move beyond the studies—this is illustrated on one of the slides presented to you—from a time when we were focused largely on Alzheimer's disease and its treatment, to the right of the slide, that is, in patients who already had the disease. Much of the goals of our research are now focused on looking at mild cognitive impairment, an earlier stage, and even at the stages before any symptoms have been developed, stages that could be identified by imaging and psychological testing, points at which intervention may be more effective than at later stages of the disease.

Among the imaging techniques which have most recently provided advances in the field is one illustrated here—for the first time, development of a series of dyes or tracers which can actually stain amyloid, one of the components of lesions commonly seen in Alzheimer's disease. So you can see in the panel on your left marked "Control," this is the PET scan or the brain image of an individual who is a control without disease, and there is very little staining—that is what the blues and greens indicate—for amyloid. In contrast, the Alzheimer's patient on the right, with red as the most intense area, shows that in a living patient, it is now possible to identify the lesions which mark the disease. The greatest utility of this potentially is to provide an opportunity for us to identify individuals with disease and to trace the process of treatment by looking at alterations in brain rather than having to wait until

they are manifest in symptoms. That is potentially accelerating the pace of developing new and effective interventions.

A year ago, we announced to the appropriations subcommittee plans for a Neuroimaging Initiative, and I am pleased to say that those plans have now been translated into reality with an initiative about to be funded in August with patients to be accrued later this year. This is an initiative that is intended to look at modalities such as PET and MRI in individuals with Alzheimer's, in those with mild cognitive impairment, and in normal individuals, to find the most precise ways by imaging all other biological markers to mark disease and disease progress.

The goal here is important. It is to find ways to identify disease early and then to most effectively identify which treatments are having an impact on the basic underlying brain changes of Alzheimer's disease. This initiative is really a remarkable collaboration of several components of NIH, together with the Food and Drug Administration who will ultimately be responsible for approving drugs that may be based on interventions using imaging such as this, the Centers for Medicare and Medicaid Services, who will be critically involved in approving the use of such agents, as well as the private sector pharmaceutical industry, who are contributing significant amounts of funding to this, and the neuroimaging industry itself.

Through all of these approaches and what has been learned about basic science, we have now developed for the first time a large number of interventions under study, illustrated here in summary, that are using agents such as anti-inflammatories, interventions designed to attack cardiovascular risk factors, and notably, ginkgo biloba, as an example of approaches to complementary and alternative medicine. We should note that this study, involving some 3,000 individuals, in collaboration with the National Center for Complementary and Alternative Medicine, is in fact the largest current clinical study of plant drugs currently under study.

This is only the beginning, and we look forward to translating the current generation of basic science into yet another iteration of effective clinical trials.

And finally, to comment on the burden that has been referred to, the important burden of caregivers. Until we have been successful in eradicating Alzheimer's disease, we also take seriously the commitment to direct research at the issue of caregiving. Most of the four million-plus Americans currently affected with Alzheimer's disease are cared for not in institutions but by family, by loved ones, individuals who themselves are subject to great stress manifest in physical as well as emotional toll. And studies such as a clinical trial called REACH, Research to Enhance Alzheimer's Caregiver Health, are currently underway in parallel with studies to approach the disease itself or those studies which tell us how to best deal with the caregiver burden that is a part of the current disease.

Again, Senator Bond, Senator Mikulski, I appreciate the opportunity to appear before you and look forward to answering any questions that you might have.

Senator BOND. Thank you very much, Dr. Hodes.

[The prepared statement of Dr. Hodes follows:]

PREPARED STATEMENT OF RICHARD J. HODES, M.D.

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. Richard Hodes, Director of the National Institute on Aging (NIA), the lead Federal agency for Alzheimer's disease research. I am delighted to be here today to tell you about the progress we are making toward understanding, treating, and preventing AD.

As you know, AD is a devastating condition with a profound impact on individuals, families, the health care system, and society as a whole. Approximately 4.5 million Americans are currently battling 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, to reverse the current trends.

Risk Factors

Many Americans wonder whether they or their loved ones are at risk of developing AD. Sadly, as they age, many of them will be. The risk of AD increases dramatically with age, with nearly half of all individuals over age 85 being diagnosed.[3] In addition, 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] In a recent review of studies of MCI and AD, investigators noted that the rate of conversion from MCI to full-blown AD ranged from 6 to 25 percent per year; in one study cited by the authors, 80 percent of MCI patients had developed AD within 6 years of their initial diagnosis.[5] 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 of three major genes for early-onset disease and have identified a major risk factor gene, ApoE4, 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.

In addition, 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 5 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. 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

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[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.

[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.

[5] Petersen RC, Stevens JC, Ganguli M, et al. "Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review)." *Neurology* 56: 1133-1142, 2001.

role of genetics in the timing of late-life forms of these devastating neurodegenerative diseases.

NIA's AD Genetics Initiative is a program to accelerate the pace of AD genetics research by creating a large repository of DNA and cell lines from families with multiple AD cases. The goal of this initiative is to develop strategies for identifying the additional late-onset AD (LOAD) risk factor genes, associated environmental factors, and the interactions of genes and the environment. The NIA's AD Genetics Initiative will intensify sample collection and encourage data sharing by providing access to a national repository to qualified investigators.

This year, we have launched several well-integrated components of the Genetics Initiative. Mechanisms to efficiently identify and share large numbers of samples for AD genetic analysis have been developed, and 18 of the NIA's Alzheimer's Disease Centers (ADCs) have received supplemental funding to recruit new family members for participation. Uniform standards for sample collection have also been developed. Recruitment is well underway; as of April, nearly 400 families, of the approximately 1,000 needed, have been evaluated and are now enrolled in the study, and over 1,000 blood samples have been collected. A major goal is the long-term follow-up of individuals participating in the study.

Investigators have also identified a number of potential lifestyle factors that may increase risk of AD, a number of which can be modified through diet or lifestyle changes. These include cardiovascular disease, high blood pressure, stroke, and history of traumatic head injury. Just over 2 years ago, researchers found that individuals with high blood levels of the amino acid homocysteine had nearly double the risk of developing AD; a trial of homocysteine-lowering agents, including vitamins B6 and B12 and folate, to slow progression of AD is currently underway. Another clinical trial is ongoing to determine whether common cholesterol-lowering drugs known as statins can slow disease progression in patients with mild to moderate AD.

Type 2 diabetes, which, according to the American Diabetes Association, affects approximately 17 million Americans, is another potential risk factor for cognitive decline and AD. In a recent study, researchers found that compared to older nondiabetic women, older women with type 2 diabetes were about 30 percent more likely to score poorly on tests of cognitive function, and that 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 nondiabetic women. Recognizing the potential link between type 2 diabetes and cognitive decline, NIA researchers are currently participating in an offshoot of the National Heart, Lung, and Blood Institute's Action to Control Cardiovascular Risk in Diabetics (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 treated with standard care guidelines is different than in people with diabetes treated with intensive care guidelines. Recruitment for the ACCORD study began in January 2003, and we anticipate that 2,800 people will participate in ACCORD-MIND.

Diagnosis

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; in fact, using the tools currently available, it may be possible to accurately diagnose AD more than 90 percent of the time.[6] Furthermore, the development of new potential methods holds tremendous promise for improved diagnosis of AD. For example, there is at present no scientifically validated method to visualize AD's characteristic amyloid plaques and neurofibrillary tangles in a living human. However, researchers have recently developed a radiotracer called Pittsburgh Compound-B that facilitates visualization of amyloid deposition in living AD patients using PET scans. Although further research is needed, such molecules may eventually offer us a powerful and accurate diagnostic tool for the disease.

Powerful imaging techniques, including positron emission tomography (PET) and magnetic resonance imaging (MRI), are opening a window into the 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 AD research.

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[6] Larson EB, Edwards JK, O'Meara E, Nochlin D, Sumi SM. Neuropathologic diagnostic outcomes from a cohort of outpatients with suspected dementia. J Gerontol A Biol Sci Med Sci 1996; 51(suppl 6):M313-M318.

Visualization of brain structures and activities may also enable us to identify people at risk of developing the disease even decades before the onset of symptoms. In a recent study, investigators used PET to examine the brains of asymptomatic young adults (ages 20–39) who were carriers of the APOE-e4 gene, a common susceptibility gene for late-onset AD. Middle-aged carriers of this gene are known to have abnormally low rates of metabolism in the same brain regions as patients with AD; in this study, the investigators found the same brain abnormalities in the younger carriers of the gene. The precise link between the APOE-e4 gene, the altered metabolism, and AD remains unknown, and more research is needed on this provocative finding, but it may offer important clues to AD's etiology and perhaps even a target for future prevention efforts.

Advances in imaging also have the potential to speed our basic understanding of the disease—for example, to determine which pathological features of AD (plaque and tangle development, cell death, loss of connections between neurons) best correlate with cognitive loss. Improved imaging techniques may further 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.

Last year, we announced our plans for a Neuroimaging Initiative, a longitudinal, prospective, natural history study of normal aging, mild cognitive impairment, and early AD to evaluate neuroimaging techniques such as MRI and PET, as well as other biological markers. I am pleased to tell you that the Initiative is underway. Awards will be made this autumn, with work on the project to begin shortly thereafter. The study objectives are to:

- Identify the best markers for early diagnosis of AD.
- Identify markers for following disease progression and monitoring treatment response.
- Develop surrogate endpoints for clinical trials.
- Decrease time and expense of drug development.
- Establish methods for the collection, processing, and distribution of neuroimaging data in conjunction with other biological, clinical, and neuropsychological data.

The initiative is planned as a partnership among the 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. The clinical, imaging, and biological data and samples will be made available, with appropriate safeguards to ensure participant privacy, to all scientific investigators in the academic and industrial research communities.

Prevention and Treatment

There is currently no available treatment for AD that is highly effective for large numbers of patients, that maintains its effectiveness for a long period, that works in both early and late stages of the disease, that improves functioning of patients in activities of daily living as well as on sensitive neuropsychological measurements, and that has no serious side effects. In addition, none of the treatments presently approved for AD alter the progressive underlying pathology of the disease. In 2003, the Food and Drug Administration approved memantine (Namenda™), the first drug to treat moderate to severe AD. Although memantine does not affect AD's underlying pathology, it can ameliorate symptoms of the disease. However, a wide variety of new treatments and approaches are emerging.

As imaging and laboratory studies tell us more about AD's pathology, we are identifying a number of novel molecular characteristics that may prove to be targets for treating the disease or preventing it altogether. For example, enhancing the brain's self-protective capacity by inducing production of naturally-occurring proteins that destroy beta amyloid shows promise in mice that have been genetically altered to produce amyloid plaques. In a recent study, boosting production of two proteins, insulin-degrading enzyme and neprilysin, in neurons of these mice reduced brain amyloid levels, slowed or even prevented amyloid plaque formation, and prevented the premature death of these mice. A similar approach—vaccination with a substance that directly attacks brain amyloid—continues to show some promise. Although a recent clinical trial was halted due to dangerous, treatment-related brain inflammation, we are hopeful that this line of research, which is being pursued by many investigators using related but alternative approaches, will ultimately yield a better, safer treatment.

Promising clinical and basic research is also ongoing on complementary and alternative (CAM) approaches to treating AD. For example, the NIA, the National Institute of Neurological Disorders and Stroke, and the National Heart, Lung, and Blood

Institute participate with the National Center for Complementary and Alternative Medicine (NCCAM) in the Ginkgo Evaluation of Memory (GEM) study, a multisite clinical trial of Ginkgo biloba for the prevention of AD in cognitively normal elders. Involving over 3,000 participants, the GEM study is the largest ongoing clinical trial of any botanical product. The NIA is also supporting a clinical trial of the effects of huperzine, a Chinese moss extract that may enhance memory and other cognitive functions by suppressing the activity of certain brain enzymes that are overactive in AD on progression of AD symptoms.

Related research is ongoing to determine Ginkgo's mechanism of action. A recent trio of NCCAM-supported studies has suggested that a standardized Ginkgo extract could protect cells from oxidative stress and programmed cell death. These studies suggest that Ginkgo may provide protection to neural tissues, adding to the body of preliminary evidence from several small clinical studies that this botanical supplement could be beneficial in preventing the onset of dementia.

In addition to these efforts, NCCAM supports a number of other AD-related studies in model systems that are designed to understand the basic mechanisms by which dietary supplements may prevent or treat the symptoms of AD. For example, NCCAM is supporting investigations of the potential mechanisms of several traditional Asian medicines used to treat AD. Also, NCCAM is supporting a study on the use of high-intensity light therapy for AD in patients in nursing homes to address the treatment of sleep/wake disorders, depressive symptoms, and agitation, among the most difficult long-term care management issues for people with AD.

In the search for effective preventives and treatments for AD, animal models—particularly transgenic mice, but also flies, worms, dogs, and even nonhuman primates—are invaluable research resources for studying age-related and disease-related changes in the brain and for testing promising interventions. For example, investigators recently studied the effects of an enriched diet on age-related cognitive decline in dogs, a model that mimics the behavioral and brain pathological declines of older humans more closely than rodent models. Young and old dogs were given a series of baseline cognitive tests. Half of each age group then remained on a standard diet, while the other half of each age group was placed on a diet enriched with antioxidants and mitochondrial co-factors, which are thought to improve nerve cell energy and efficiency and decrease production of molecules that contribute to oxidative damage in the brain. Animals remained on their respective diets for 6 months and then were assessed again for cognitive performance on a variety of tasks. When tested, old dogs on the control diet learned more slowly than the young dogs and made significantly more errors; however, when compared to the old animals on the control diet, old animals on the enriched diet showed significantly better learning, although not to the level of the younger animals. The success of this simple, cost-effective intervention has significant implications for dietary interventions that might lessen or even prevent some of the cognitive decline seen with age and with disease; several clinical trials of antioxidants are currently underway.

The NIA is currently supporting over 20 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.

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. Caregivers frequently experience significant emotional stress, physical strain, and financial burdens, yet they often do not receive adequate support for their remarkable efforts. Several recent studies have explored the problems faced by caregivers of AD patients, and have sought to design interventions to reduce their burdens. Although family caregiving has been extensively studied, there has been less research on the impact of end-of-patient-life on caregivers who are family members of persons with dementia or to the caregivers' responses to the death of the patient. As part of the NIA's Resources for Enhancing Alzheimer's Caregiver Health (REACH) study, a multisite randomized clinical intervention of 1,222 caregiver and recipient dyads, investigators assessed the type and intensity of care provided by 217 family caregivers to persons with dementia during the year before the patient's death, as well as the caregivers' responses to the death. Additionally, this group was compared to the 180 caregivers who institutionalized their family member. The researchers found that the in-home caregivers reported tremendous levels of stress in the year leading up to the care recipient's death, and that levels of caregiver depression

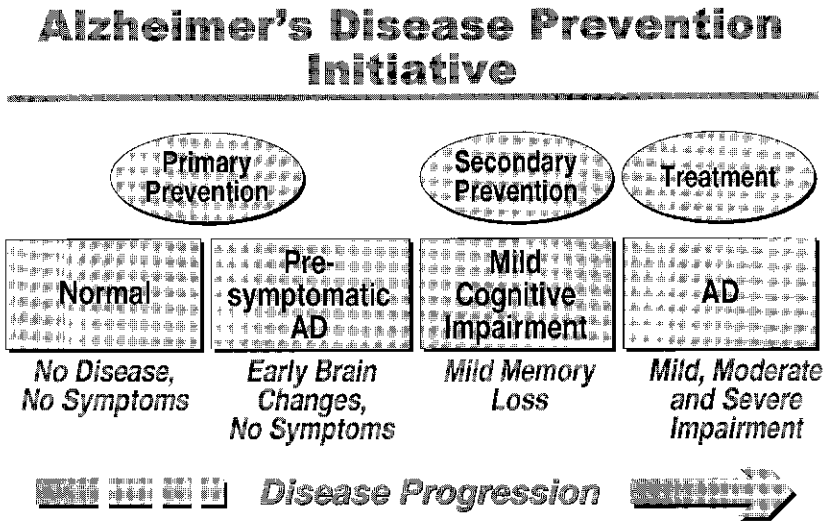
"spiked" immediately following the care recipient death. However, the caregivers in this study demonstrated tremendous resilience: Within 15 weeks of the recipient's death, depression returned to pre-death levels, and within 1 year, depression was significantly lower than prior to the care recipients' death. Importantly, caregiver depression for those placing their loved ones in an institution was slightly higher both pre- and postdeath than for those caring for the patient at home. These findings suggest that interventions for caregiver support are particularly critical in the periods immediately prior to and immediately after the patient's death.

The NIA's REACH Project, a large, multisite intervention study of family caregivers of AD patients, was designed to characterize and test promising interventions for enhancing family caregiving. Nine different social and behavioral interventions were tested, and investigators found that the combined effect of certain interventions alleviated caregiver burden, and that certain specific interventions, such as structured family therapy, reduced depression. The second phase of the study, REACH II, combines elements of the most effective interventions tested in REACH into a single multicomponent psychosocial intervention and is ongoing.

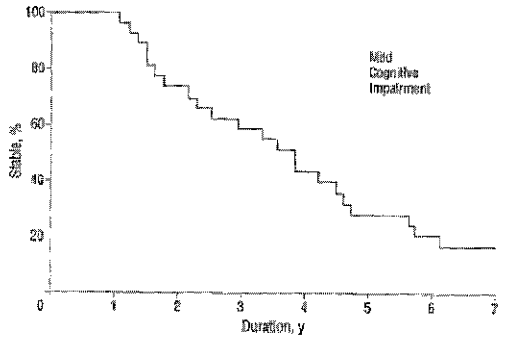
Conclusion

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 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.



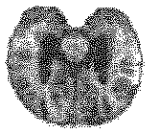
Risk of Developing Alzheimer's Disease in Persons with MCI



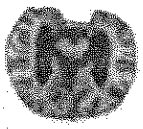
Survival curve of persons characterized as having a mild cognitive impairment for 6 years. Approximately 80% have converted to dementia during this time.

Peterson RC, et al., *Arch Neurol.* 58:1985-1992, 2001.

Volume of Hippocampus and Rate of Shrinkage Predicts Crossover from MCI to AD



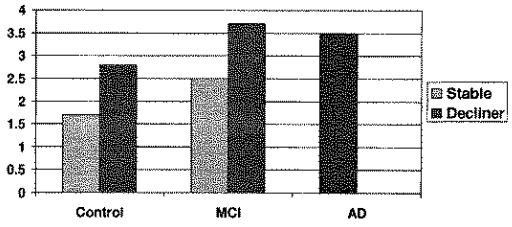
Normal, 75 years old



Alzheimer's disease, 75 years old

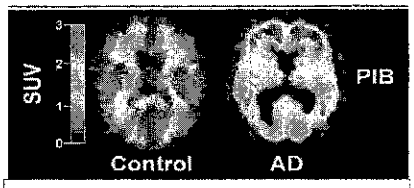
De Leon MJ, 1999

Percent Annual Decline in Hippocampal Volume



Jack CR, et al, Neurology 55: 484-489, 2000

PET Imaging of Amyloid Deposits in Alzheimer's Disease vs Normal Controls



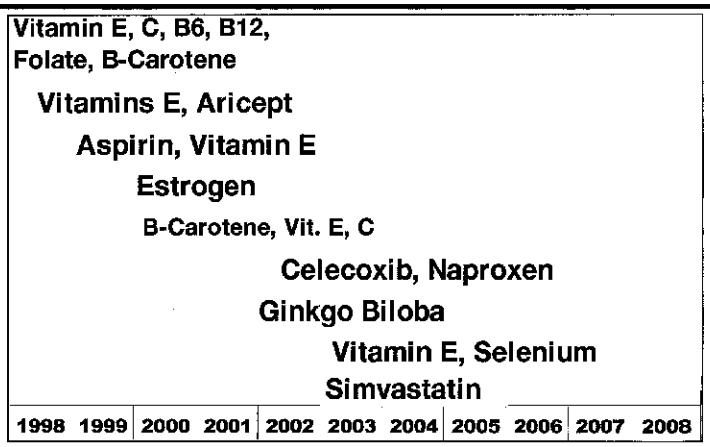
PET imaging with a novel tracer, Pittsburgh Compound-B (PIB), can provide quantitative information on amyloid deposits in living subjects.

Source: Klunk, et al. *Ann Neurol* 2004; 55:306-319.

Current Drug Treatments for AD

- Acetylcholinesterase inhibitors for mild to moderate AD
  - Tacrine (Cognex)
  - Denepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Reminyl)
- Neuroprotective agent for moderate to severe AD
  - Memantine (Namenda)

Funded AD Prevention and Selected Treatment Trials



April 2002

Complementary & Alternative Therapies for AD

- Ginkgo Evaluation of Memory (GEM) study
- Clinical trial of huperzine
- Traditional Asian medicines
- High intensity light therapy

REACH II Intervention

The REACH II intervention is a multi-component intervention designed to address five areas linked to caregiver risk profile:

- Safety
- Social Support
- CR Problem Behaviors
- Emotional well-being
- Self-care and Health Behaviors

Senator BOND. Dr. Morris?

Dr. MORRIS. Senator Bond, Senator Mikulski, thank you very much for the opportunity to appear here.

I am a neurologist taking care of Alzheimer's patients and their families. I also direct the Alzheimer's Disease Research Center at Washington University in St. Louis, and I am a member of the national board of the Alzheimer's Association. So I have a variety of opportunities to interact with Alzheimer's on a daily basis.

The Alzheimer's disease research centers were first funded in 1984, and in the past 20 years, the centers and related programs have learned a great deal about Alzheimer's disease.

First, we now know that it is just that—it is a disease. It is not part of normal aging. As a disease, it can be diagnosed, and indeed we can diagnose Alzheimer's disease with high accuracy. We have learned even to extend the diagnosis to the initial symptomatic stages, sometimes even in the mild cognitive impairment stage.

So it can be recognized and accurately diagnosed very early. Unfortunately, many people are unaware of this and still believe that Alzheimer's disease is inevitable with age, it is part of the aging process, and even though the diagnostic opportunities are there to recognize it, many physicians and many families are unaware of this.

As a matter of fact, Alzheimer's disease is woefully underdiagnosed in the United States, even with our accurate diagnostic tools. The tragedy of that is that without recognizing it, it is woefully undertreated. We do have treatments available to help the symptoms of Alzheimer's disease. Alzheimer's disease is a treatable disorder. So we need to get the word out to better recognize it and to better treat the symptoms.

Now, it is true that the current therapies only help the symptoms, and only for a limited time. So the vast majority of research is interested in looking at interventions that will help the very brain changes that cause the disease—interventions to affect the disease process, to arrest it, and hopefully even to prevent it.

But to do that, we need to understand the disease process even before symptoms appear. It is very likely—very likely—that Alz-

heimer's disease changes begin in the brain years or even decades before any dementia appears. It is possible that the illness begins in middle age or even earlier. And if we ever want to prevent the disease, we have to recognize those brain changes at the asymptomatic stage and intervene there to prevent the occurrence of dementia symptoms from appearing.

There are very exciting, very innovative medications that potentially have the promise of intervening at that early stage, and as Dr. Hodes indicated with his imaging work, in fact there may be opportunities to detect the disease in the pre-symptomatic stage.

Much research is focused upon this effort. For example, at our Alzheimer's center, we have inaugurated an adult children study with children whose parents had Alzheimer's disease, who are participating in all of these research ventures to see what are the earliest changes that may occur so that when these disease-modifying therapies are available, we know with whom to intervene at the most opportune time.

Unfortunately, with the budget slowdown, these and other research efforts are having to be truncated. It is a remarkable time in Alzheimer's disease research. The past 20 years have yielded remarkable advances, and in addition, they have provided us with the research infrastructure to test all of these new opportunities and new hypotheses. We have the investigators, we have the research participants, we have the drugs, we have the desire to see if we can arrest or cure Alzheimer's disease.

So this is the time to take advantage of all the investment of the past 20 years. Unfortunately, some of these initiatives are going to have to be truncated if we do not continue to invest in trying to develop a world without Alzheimer's disease.

Thank you very much.

Senator BOND. Thank you, Dr. Morris.

[The prepared statement of Dr. Morris follows:]

PREPARED STATEMENT OF JOHN C. MORRIS, M.D.

The rapidly growing older adult population has resulted in dramatic increases in age-associated illnesses, most notably the dementing disorders. Dementia affects 10 percent of all individuals 65 years or older, and its prevalence rises exponentially to approach 50 percent by age 85. Dementia is costly, both in terms of public health burden ($100 billion annually in the U.S.) and in the personal toll extracted from patients and their families. As U.S. society continues to age, the already major impact of dementia soon will become overwhelming unless effective interventions become available.

There have been remarkable clinical and research advances in dementia in the past 2 decades. It is now appreciated that dementia is not part of normal aging but instead represents a disease process. Although a diagnostic test or biomarker is lacking for most dementing disorders, clinical diagnosis can be surprisingly accurate. Most importantly, effective therapeutic options are now available for Alzheimer disease (AD), by far the most common cause of dementia—AD now is a treatable disorder! The availability of treatments has led to improved detection of dementia in its earliest stages and stimulated great interest in prodromal conditions, such as mild cognitive impairment.

Currently approved drugs provide symptomatic benefit for AD. Although the effect size is modest, their benefit is appreciated by physicians and families and can be demonstrated for periods extending beyond 1 year. Many other agents are being tested in clinical trials. Recent drug development efforts are directed toward disease-modifying strategies. Should one or more of these approaches prove safe and effective, it may become possible to arrest the progression of AD or even to prevent its occurrence.

The optimal time to initiate prevention strategies is in the latent or preclinical stages of AD, prior to the occurrence of any symptoms. It is possible that Alzheimer's begins in the brain years or even decades before sufficient damage occurs to allow dementia symptoms to be expressed. Because the diagnosis of AD currently depends on these symptoms, detection of the preclinical stages is not possible at present. However, highly promising new strategies, including identifying Alzheimer brain changes with imaging techniques in asymptomatic persons, now are under investigation. A very reasonable prediction is that, in the not too distant future, persons at risk for developing AD because of family history or other factors can be assessed before symptoms appear. If they have suggestive brain changes, ideally they would be offered therapies that prevent the development of dementia!

This is a propitious time to pursue the tremendous opportunities for the effective treatment, prevention, and even cure of AD. The appropriate infrastructure is in place with ample numbers of patients, investigators, and assessment tools to test the many promising therapeutic agents now being developed. The only limiting factor is a lack of funds to carry out these innovative research studies that hold potentially enormous consequences for patients and for society.

Senator BOND. Dr. Rabins?

Dr. RABINS. Thank you, Senator Bond, Senator Mikulski.

I would like to address the currently available treatments, the potential for prevention, and where I see the future in Alzheimer's disease research.

Right now, there are two classes of medicines that are used to treat Alzheimer's disease, and both of these classes actually depend on breakthroughs that were made back in the 1970's. In the early 1970's in this country and in England, it was discovered that individuals dying with Alzheimer's disease have a deficiency of a particular chemical called acetylcholine in their brains. Three of the medicines that are widely used now to treat Alzheimer's disease all work by increasing the amount of that chemical.

The second class of medicines that is now used to treat Alzheimer's disease also derives from breakthroughs in the 1970's, both at Washington University and Johns Hopkins. This research showed that when the cells that make chemicals like acetylcholine do not make enough, the receiving cells send a message back saying: Send more, send more. That is, they excite the other cell. Unfortunately, when they do not get enough, they overexcite the cell to the point where they actually cause death. So the body's attempt to recover from a lack of this acetylcholine chemical actually causes overexcitement of these remaining cells and then leads to death. So the second class of medicines, the first one of which was just recently approved by the FDA, works by dampening how the body tries to restimulate it.

So those are the two classes of medications, both depending on research breakthroughs from the 1970's.

I think what is exciting, as Dr. Hodes said, is that what has happened in the last 20 years is that we now understand, we think, what is actually happening inside the brains of people with Alzheimer's disease. The leading theory of the cause is that abnormal proteins are being deposited in the brain. And I think what is very exciting now—and I would like to take Dr. Morris' use of the word "remarkable"—is that the opportunities that we have now are to interfere with the deposition of these abnormal proteins in such a way that perhaps they could be removed from the brain or at least the deposition could be slowed down or prevented. We are at a point in time when there are many different opportunities, and a number of biotech companies, pharmaceutical companies, but a lot

of this work is so basic that it really depends on NIH funding, and I think we are at a crucial point where many of these new opportunities will not be followed through, such as chelation therapy for some of the ions and metals that may be involved—that we will lose those opportunities for developing treatments.

As far as prevention, we are also at an exciting time, and I would just like to very briefly highlight four potential prevention strategies.

The first, as Dr. Hodes mentioned, it is clear now that the risk factors for cardiovascular disease—that is, high blood pressure, high cholesterol, obesity, and diabetes—when those appear to be aggressively treated, it appears that we can actually decrease the likelihood of developing Alzheimer's disease. So in that way, we have opportunities now to begin with prevention.

A second intriguing area is that many studies have suggested that drugs like Motrin, nonsteroidal anti-inflammatory drugs, may be preventive, and there is a very large trial funded by the National Institute on Aging that is looking at whether taking several of these medications might actually delay the onset of Alzheimer's disease. So we will have an answer to that in several years.

I think, as Dr. Hodes also mentioned, the area of genetics is extremely important. People tend to think of genetics as something that we will not be able to change, but with a disease like Alzheimer's disease that does not begin for 50, 60, or 70 years, if we could understand the genetics of this illness, that would offer us actual opportunities to develop drugs and other preventive strategies even if you carry a genetic risk factor. So I think that is very exciting.

Then, the fourth area, which builds on something that Senator Mikulski mentioned, is the whole issue of whether exercise, physical exercise, and mental activity might be able to delay the onset of Alzheimer's disease, and there are a number of studies that suggest that possibility. I think the need for further trials in that area is important.

I think we are at the crucial point now in the development of treatments and preventions, and I think that with further funding, the possibility of a breakthrough that will diminish both the burden of family and this tremendous financial burden is great.

Senator BOND. Thank you very much, Dr. Rabins.

[The prepared statement of Dr. Rabins follows:]

PREPARED STATEMENT OF PETER V. RABINS, M.D.

Honorable Senators and other attendees. In my testimony I will address the availability and adequacy of current treatments for Alzheimer disease, the potential for preventing Alzheimer disease and the importance of continued support for research and care into this devastating, common illness.

Descriptions of Alzheimer disease are contained in the earliest medical writings that are 3,000 years old. However, the brain changes characteristic of Alzheimer disease were described only 100 years ago and it has only been in the past 35 years that clinicians, scientists and the public have appreciated the fact that what used to be called "senility" is a group of diseases referred to medically as dementias. Today we recognize that two-thirds of all cases of late life dementing is caused by Alzheimer disease.

CURRENTLY AVAILABLE TREATMENTS

The recognition that "senility" is most commonly caused by Alzheimer disease led to the discovery in the mid-1970s by researchers in Europe and the United States

that a chemical called acetylcholine is deficient in the brains of individuals dying from the illness. Three of the treatments that are available today, donepezil (Aricept), galantamine (Reminyl) and rivastigmine (Excelon) work by increasing the amount of this chemical in the brain. These medications are all modestly effective in treating patients with Alzheimer disease; this benefit translates into improved function, behavior and cognition (thinking). On average, these drugs bring about a 6–9 month improvement in the disease. However, they do not modify the underlying biology; the death of brain cells due to the disorder continues in spite of treatment. It is important to emphasize that the modest benefit provided by these medications translates into meaningful improvement and, equally importantly, demonstrates that the symptoms of the disease are amenable to biological therapies.

A second class of medications builds upon the discovery made at Washington University, St. Louis and Johns Hopkins that the brain responds to loss of acetylcholine by stimulating or "exciting" the remaining cells with the neurotransmitter glutamate. Unfortunately, this results in "excito-toxicity" due to overstimulation of these remaining cells. The first example of this class of medications, memantine, (Namenda) was developed in Germany and recently approved by the FDA for the treatment of individuals with moderate-severe Alzheimer. It is hoped that disease progression might be slowed by blocking glutamate but this has not yet been proven.

POTENTIAL TREATMENTS

Tremendous strides have been made in the past 25 years in understanding the basic biology of memory and other thinking processes. Drugs are under development that seek to enhance these processes. In addition, an extensive body of research has focused on the function and metabolism of the proteins thought to be involved in the genesis of Alzheimer disease. Studies funded by the NIA, NINDS and NIMH suggest that the deposition of abnormal proteins may be the initiating and/or perpetuating cause of Alzheimer disease. Many pharmaceutical companies, biotech companies and publicly funded researchers are studying compounds that potentially interfere with the formation or deposition of these abnormal proteins, or might increase their removal from the brain. Studies of the effectiveness of these therapies has begun only recently, but the quality of research being performed now is quite extraordinary and many scientists believe that therapies that target the biology of the disease and slow its development, stop its development or reverse the abnormalities are a possibility. NIH-sponsored research has played a major role in the development of many of these approaches.

TREATMENT

Extensive nondrug research demonstrates the benefit of interventions that provide information and emotional support to caregivers. Intriguingly, these interventions have been shown to have 3 benefits, improving the psychological well-being of the caregiver, diminishing the prevalence of behavioral and psychiatric symptoms in the patient and delaying placement in a long-term care facility, a goal of many family members and patients. Much of this research has been supported by the NIH.

PREVENTION

At present, the best supported preventive strategy for Alzheimer disease is treating the risk factors for brain vascular disease—controlling high blood pressure, elevated cholesterol, elevated low density level lipoprotein (LDL) levels, diabetes and obesity. The contribution of these to the development of Alzheimer disease may be modest but they could have a meaningful impact because so many people are affected.

A second potential prevention strategy is the use of nonsteroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen (Motrin, Advil and generic). At present, the studies supporting the preventive actions of the drugs in this class are all retrospective. That is, they depend on data collected from individuals who do have Alzheimer disease and do not have Alzheimer disease. A prospective trial (funded by the NIA) called ADAPT should tell us in several years whether drugs in this class can delay the onset or prevent Alzheimer disease. It now appears that women who take hormone replacement therapy after age 64 are at increased risk of developing Alzheimer disease. However, some research suggests that estrogen taken at the time of menopause may be preventive. More research is needed on this topic.

A third area of research that has potential for prevention is the study of genetic risk factors. This may reveal targets for medication that can prevent or delay the onset of disease.

A fourth area of intense interest and scrutiny is whether mental and/or physical activity lowers the risk of developing Alzheimer disease. To date, studies supporting this are all retrospective and thus can only suggest the possibility of such a benefit. Some research also suggests that more years of education offers some protection and some individuals raise the possibility that this may work by increasing connections among brain cells.

FUTURE PROSPECTS

In my opinion we are at a crucial point in the development of therapies aimed at altering the biology of Alzheimer disease. Whether such a treatment will be available in 5 years or 50 years cannot be foreseen, but the pace of research and the advances already made increase the likelihood that a disease-altering or preventing therapy will be identified. In my opinion, the need or continued research in this area should remain a high priority, given the devastation wrought by this illness on individual Americans and their family members as well as the economic costs of the disease. In many States, Medicaid nursing home benefits are one of the largest individual budget items and Alzheimer disease is the single greatest contributor to nursing home placement in the U.S.

Research should also continue to look for better strategies to diminish the emotional, financial and behavioral burdens wrought by the dementias until cures and preventions are available. This important work complements research into the basic biology of the disease and the development of more biological effects therapies.

As a clinician and clinical researcher for 30 years, I have watched Alzheimer disease change from a condition known to a handful of experts to a disorder that is feared universally. Only through continued research can these fears and burdens be relieved. The need for such research is shown in a study that I have just completed which demonstrates that fewer than ⅓ of people with Alzheimer disease who live at home are recognized by their doctor as having dementia.

Senator BOND. Mr. McConnell?

Mr. MCCONNELL. Senator Bond, Senator Mikulski, thank you for inviting the Alzheimer's Association to this hearing.

This is a very important topic that comes at a critical time. You both pointed out this epidemic, really, of 4.5 million now, growing to as many as 16 million. There is a new Neurology Journal study coming out today showing the increases by State, an 18 percent increase in the next 20 years in Missouri and a 25 percent increase in Maryland during that period of time.

The impact on Medicaid and Medicare is enormous. The cost for just treating Alzheimer's disease in Medicare will go up 55 percent in this decade to $50 billion, and for Medicaid, an increase of 80 percent to $33 billion. That is just for treating Alzheimer's disease. So this is not just a matter of a science question; it is a matter of public health and huge impact on Federal programs.

Having said that, there is an enormous amount of hope. You have heard that from the scientists to my left. And we are trying to get that message out to the public. The Alzheimer's Association has launched a Maintain Your Brain Campaign—I have a brochure here; the ink is still drying on it—taking what we have learned in science and trying to get it out to, for one thing, the 78 million baby boomers who are living in denial. That is my age cohort, and the baby boomers say this is an issue that we cannot do anything about, it is inevitable, and we are going to turn off to it.

So we are trying to say no—there is an enormous amount that can be done. Dr. Rabins has talked about it; all of the scientists here have talked about it.

No. 1, we say manage your numbers. As Dr. Rabins pointed out, the linkage between cardiovascular disease and Alzheimer's disease is becoming clearer. Keep your blood pressure under control, your cholesterol, your blood sugar, your body weight. We do not know

that those will prevent Alzheimer's disease, but they cannot hurt, and there is some evidence that it may help in preventing Alzheimer's.

Second, feed your brain—a multivitamin with folic acid, vitamin E, vitamin C. Eat foods right in Omega-3 fatty acids.

Third, exercise your body and brain by working out, taking a class, reading, playing cards. I love the study that came out recently that shows that dancing may actually be preventive—and I suspect that is only if you are a good dancer—but nonetheless, these are simple things that are about keeping your heart and your body healthy that may keep your brain healthy.

But the public does not understand this and still thinks there is not much that can be done.

All of this progress has been made because of your efforts to double the NIH funding, which has also doubled research funding for Alzheimer's disease. That is now starting to taper off, and we are already starting to see a tapering off in what NIA can fund. They can fund fewer grants; they have to fund them at a smaller level. There are research projects at UC-San Diego on combination therapies that will not go forward because there is not enough funding.

So the Alzheimer's Association is asking for a modest increase of $40 million to the $670 million a year that is being spent on Alzheimer's disease so we can keep this progress going. Otherwise, our investment will be for naught.

I do want to point out the second part of our mission and also of this hearing is on caregiving. The Alzheimer's Association is committed to helping families and people with this disease through our chapters. We have a 24/7 contact center; people can call in the middle of the night if they are having a crisis and get help. We have clinical social workers on that line, and that is also being supported in part by your efforts and appropriations.

We know that caregiving particularly for people with Alzheimer's disease is enormously stressful. There are greater stress-related illnesses and even higher mortality rates because of caregiving for Alzheimer's disease. So we need to help families, and I particularly want to acknowledge, Senator Mikulski, your bill, the Family Caregiver Relief Act of 2003, the $5,000 tax credit. That not only will help people by providing them with resources, but it legitimizes caregiving. People are out there struggling with this stuff by themselves, and in this case, if there is a tax credit, it says, you know, this is an important enough issue that the Government cares enough about it to give us a tax credit, it helps people psychologically and otherwise.

The Alzheimer's Disease Research, Prevention, and Care Act of 2003, the Alzheimer's Demonstration Grants, which are leading the way in finding ways to deliver services, particularly respite and home and community-based services, to underserved communities. There is a project in Missouri, and there is a project in Maryland under this grant, and it is producing terrific results.

So we have to keep going forward on the research front. We need to make sure that the information gets out to the public, and hearings like this can help educate people on what needs to be done. But if we do not have the funding to keep this progress moving—just for example, the ginkgo biloba trial that was mentioned by Dr.

Hodes is $30 million to do that one trial. So if we can only do one trial at a time and wait to see the results, we will not get this problem taken care of before that baby boom population hits the age of highest risk.

So again, there is enormous hope, more and more help for caregivers, but we are still on the cusp of those major breakthroughs, and the Alzheimer's Association is very optimistic. We do our part—we have committed $150 million to this research effort—and we thank you for all that you are doing.

[The prepared statement of Mr. McConnell follows:]

PREPARED STATEMENT OF STEPHEN MCCONNELL

Good morning Senator Bond and Senator Mikulski. Thank you for inviting me to discuss the Alzheimer's Association's legislative priorities as well as our exciting new "Maintain Your Brain" initiative. I want to acknowledge the outstanding leadership that both of you have provided in the fight against Alzheimer's disease. The Alzheimer's Association especially appreciates your commitment and dedication to improving care and services for individuals with Alzheimer's disease and their caregivers. We thank you for introducing S. 566, *the Alzheimer's Disease Research, Prevention & Care Act*, legislation to renew a highly successful program that is providing Federal grants to States to develop innovative models of care for persons with Alzheimer's disease. In addition, we are indebted to Senator Mikulski and other Members of this Subcommittee who are cosponsoring S. 538, *the Lifespan Respite Care Act*, and S. 1214, *the Family Caregiver Relief Act*, proposals to increase the availability of respite care services and create a tax credit for family caregivers.

Since our founding in 1980, the Alzheimer's Association has provided more than $150 million to support research into the prevention, treatment and eventual cure for Alzheimer's. Our nationwide network of chapters offer frontline support to individuals affected by Alzheimer's with services that include 24/7 information and referral, safety services, and education and support groups. In addition, we are partnering with over 150 local, State and national organizations representing more than 50 million Americans on our "Coalition of Hope", the largest Coalition ever formed in support of research to find new treatments for individuals with Alzheimer's disease. The Coalition of Hope includes groups well known in the aging field, including AARP, the Older Women's League and the National Association of Retired Federal Employees. It also includes other organizations like the Urban League, the Polish American Congress, the NAACP and the Sons of Italy, who know that Alzheimer's touches so many families and communities, in small towns and big cities all across the country.

The mission of the Alzheimer's Association, working in partnership with government and private industry, is to eradicate this disease and to provide support to improve quality of life for those facing the disease now. Through the combined efforts of the Association, the National Institutes of Health, and the pharmaceutical industry, advances in medical treatment have surged forward in recent years. The Alzheimer's Association's goal of delaying the disabling symptoms of Alzheimer's disease, and eventually preventing the disease now appears possible. For the first time, creating "A World Without Alzheimer's" is within reach. We can go to the American people now with a new message of hope. We can—we will—have a future where Alzheimer's disease is only a memory.

This hearing comes at a critical time. With the aging of the baby boomers, the number of people with Alzheimer's will grow from 4.5 million today to an astounding 11 to 16 million by the middle of the century. Today's issue of *Neurology* features a new study estimating state-specific projections of the prevalence of Alzheimer's disease through 2025. Although the study found that the greatest rates of growth in the number of cases of Alzheimer's disease will be seen in the Southern and Western regions of the country, few States will be spared from the impact of Alzheimer's disease. Missouri will see an 18 percent increase in the number of cases of Alzheimer's disease. Maryland faces an even greater rate of growth—28 percent by 2025. Left unchecked, Alzheimer's will undermine our families, communities, and basic economic security. It will overwhelm our health care system, bankrupt Medicare and Medicaid, drain billions of dollars from American business, and destroy retirement security for tens of millions of families. The cost to Medicare will go up 55 percent to $50 billion in less than 10 years and the cost to Medicaid will soar by 80 percent to $33 billion. The costs to families and caregivers will go even higher.

We can treat Alzheimer's and some day we may be able to prevent this disease, but not without more funds for research and greater help from Congress. If the current pace and momentum of research is maintained we may be able to delay the onset and progression of Alzheimer's, saving not only billions of dollars to our health care system but also saving millions of lives. This is not the time to tell the scientists to slow down. But this is exactly what will happen unless we continue to expand the public investment in Alzheimer research.

News You Can Use: The Maintain Your Brain™ Campaign

The title of this hearing, "Breakthroughs in Alzheimer's Research: News You Can Use" is particularly relevant to an effort underway to change the way Americans think about Alzheimer's disease. Thanks to the rapid progress being made in understanding, diagnosing and treating Alzheimer's disease, we can share the news that Alzheimer's disease is not an inevitable part of aging. Earlier this year, the Alzheimer's Association launched a new Maintain Your Brain™ campaign to let the public know that a world without Alzheimer's disease can be a reality, to encourage Americans to take steps now to take care of their brain and to engage more people in advocacy for research, new treatments and improved care.

The Maintain Your Brain™ campaign is targeted to the 77 million American baby boomers to encourage them—I should say "us"—to get involved. To date, baby boomers have largely ignored Alzheimer's disease because they don't think there is anything you can do about it. Our campaign is designed to change that before we enter the age of greatest risk for dementia. If we are successful, we may be able to avoid some of the devastating problems that are looming on the horizon.

Our Maintain Your Brain Campaign is based on the mounting evidence that we can manage certain risk factors and maintain optimal brain functions. Just as we can take steps to preserve a healthy heart, we can manage certain risk factors to maintain a healthy brain. Manage your numbers—blood pressure, cholesterol, blood sugar and body weight—to stay healthy as you age. Feed your brain by taking a multivitamin that includes folic acid, vitamins E and C and eat foods rich in omega-3 fatty acids. Exercise both your body and brain by working out, taking a class, reading, playing cards or working on crossword puzzles. Know that the joint efforts of government agencies, research centers and pharmaceutical companies have uncovered many of the secrets of Alzheimer's disease and that there are many reasons to be hopeful. And, perhaps most importantly, get involved in advocacy for more research, improved treatments, and better care.

The Alzheimer Research Agenda

Most scientists believe that discovering effective methods and treatments that will delay the onset and progression of Alzheimer's as well as prevent the disease are well within reach in the foreseeable future if the current pace and momentum of research is maintained. Research supported by the National Institutes of Health needs $40 million in additional funding this fiscal year alone to carry out large scale, controlled, clinical trials that will identify therapies and treatments capable of slowing or halting the onset and progression of Alzheimer's. Basic research has produced positive discoveries, but we need to know whether the discoveries will actually work. Clinical trials are the only way to translate—and verify—the findings of basic research into real-world treatments. A single large-scale clinical trial could cost as much as $25 million and take 3 to 5 years. The Alzheimer's Association is asking Congress to increase funding for Alzheimer research by $40 million for fiscal year 2005 to fund large-scale clinical trials to test the effectiveness of vitamins and other treatments that would slow or delay the progression of Alzheimer's.

While we maintain hope about our ability to slow the progression of and 1 day prevent Alzheimer's disease, we must also invest in research that will speed the discovery of risk factor genes for late-onset Alzheimer's, the most common form of the disease. Discovery of risk factor genes will help illuminate the underlying disease processes of Alzheimer's disease, open up novel areas of research and identify new targets for drug therapy. The National Institute on Aging (NIA) and the Alzheimer's Association are in the process of recruiting at least 1,000 families over the next 3 years to create the Nation's largest repository of genetic material from families affected by late-onset Alzheimer's disease.

The National Institute on Aging, in partnership with the pharmaceutical industry, the Alzheimer's Association and the FDA, is also engaged in a new initiative using imaging technologies to monitor changes in the brain that indicate progression of Alzheimer's disease and to provide accurate, earlier diagnosis. We are hopeful that this initiative will lead to better diagnostic techniques. More importantly, the imaging initiative may help speed up the process of discovering new, more effective treatments and preventive agents for Alzheimer's disease by allowing scientists to detect

the effects of interventions on brain function much more quickly than traditional clinical trials without the use of imaging. The full participation of the pharmaceutical industry and the FDA will ensure that we gain maximum effect from this important initiative.

Supporting A Public/Private Partnership

The Alzheimer's Association is the largest private funder of Alzheimer research, next to the pharmaceutical industry. As our commitment to research has grown, we have expanded the program to support Alzheimer researchers at every stage in their career. Projects supported by the Alzheimer's Association research program now explore the broadest possible spectrum of biological approaches to understanding, preventing, and treating Alzheimer's. In addition to our support of medical research, the Association also invests in improving care, with research grants supporting efforts to develop innovative social and behavioral strategies for managing the symptoms of the disease and improving quality of life, approaches to caregiving and improved understanding of caregiver issues.

Our goal is to support research that complements the programs of the National Institute on Aging (NIA) and other centers of the National Institutes of Health (NIH). Our research program is designed to serve as an incubator for innovative ideas that can be further enhanced by the tremendous resources only available through NIH and its national network of Alzheimer's Disease Centers.

Many of this country's premier Alzheimer researchers got their start with funds from the Alzheimer's Association. Alzheimer researchers funded by the Association have gone on to acquire major Federal funding, originate and advocate for important areas of research, train the next generation of scientists, establish many of the Alzheimer's Disease Research Centers and direct key programs at NIA. These researchers include brilliant scientists such as Dennis Selkoe, whose early work on amyloid proteins helped define our current understanding of Alzheimer's disease, Caleb Finch, who is the director of the Alzheimer's Disease Research Center at the University of Southern California, Gary Small, a leader in the imaging field and Marcelle Morrison Bogorad, who as an integral part of Dr. Hodes' team, directs the Neuroscience and Neuropsychology of Aging Program at NIA.

In addition to partnering with NIA and other centers at NIH, the Alzheimer's Association also plays a major role in bringing the Alzheimer research community together for scientific meetings. In July we will present the ninth annual International Conference on Alzheimer's Disease and Related Disorders, the world's leading forum on dementia research. The International Conference serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community. Approximately 4,500 researchers, double the number who attended the July 2000 meeting in Washington, will gather in Philadelphia to share groundbreaking information and resources on the etiology, pathology and treatment of Alzheimer's disease and related disorders. The program will include 135 invited speakers, who are respected leaders and new voices in their disciplines, and more than 2,000 oral and poster presentations on current research. The conference also provides a significant opportunity to educate the public about breakthroughs in Alzheimer treatment and care.

A Roadblock to Progress

All of the hope we have for a future without Alzheimer's disease will come to a crashing halt if we cannot maintain the current pace and momentum of funding for Alzheimer research. Only Congress and the President, through a significant addition of new funding, can assure that we realize the unprecedented opportunities in Alzheimer research. Minimal increases in funding for the NIH are not enough to support additional clinical trials and maintain the pipeline of basic scientific discovery. Failure to provide the funding increases that will help keep pace with inflation will destroy the momentum gained over the past 5 years. Inadequate funding increases mean that less money will be available to support new research grants and clinical trials, delaying scientific discoveries and resulting in lost opportunities.

Although I am not a scientist, I have spent a lot of time talking with scientists. Let me give you just a few examples of the opportunities we will miss if we stick with current and proposed funding levels:

• Thanks to Congress' investment in NIH, the best scientists in the world are chomping at the Alzheimer bit—and that means NIA is receiving record numbers of applications. But at current budgets, they will be able to fund only about 15 percent of those proposals—far less than the 20—25 percent of past years. And they can only do that much by cutting one of every five dollars out of the successful grants. Think about how many scientific opportunities we are missing.

• What about the large scale clinical trials in which Congress has invested billions of dollars? After all, research doesn't mean a lot in the real world until we are successful in getting science from the bench to the bedside.

• Scientists at the University of California in San Diego are poised to start the next big trial of combinations of anti-oxidants. This offers one of the most exciting possibilities for a safe and relatively inexpensive way to protect against Alzheimer's. But NIA does not have the money to get it started.

• Even trials that are well underway—like the ginko biloba trial being conducted through a collaborative effort between NIA and NCCAM—will have to be slowed down. There may be no money to analyze the data that has already been collected on the hundreds of volunteers who have participated in this trial.

• NIA currently funds 29 Alzheimer's Disease Research Centers, a program that has created the infrastructure for multidisciplinary collaborative research on the disease. NIA has seen an increasing number of applications from academic institutions seeking to create such centers and there are still parts of the country where Centers do not exist. Limited funding will make the competition for center grants especially tough this year. At the same time, we have heard that existing centers are increasingly strapped for funds to carry out their broad mission.

This is a travesty. We cannot let it happen. We know that Congress faces many competing priorities, with very little discretionary money in the budget. We understand that, after doubling the NIH budget, there are those who are ready to say, "we've done enough." But if we slow down now, we will be throwing away much of the investment the American taxpayers have already made in Alzheimer research. We must continue, and build on, the progress of the last 20 years. That is why we are asking you to increase funding for Alzheimer research by $40 million for fiscal year 2005. This is a modest request, given the urgency of the Alzheimer crisis and the enormity of the scientific opportunities. But it would be enough to sustain the momentum in tough budget times. The *Neurology* study on the growth in the prevalence of Alzheimer's disease by State that I cited earlier provides further evidence of the need to invest in the research that will help prevent or delay the onset of Alzheimer's disease. The study found that five States (Utah, Alaska, Colorado, Wyoming and Nevada) will see their total number of cases of Alzheimer's disease more than double between 2000 and 2025. The three largest States will also experience big increases in the number of cases of Alzheimer's disease—California faces a 50 percent increase, Florida a 64 percent increase and Texas a 74 percent increase. The best way to ensure that these estimates do not come true is to find an effective method of preventing Alzheimer's disease.

Taking Care of People With Alzheimer's & Their Caregivers: Social & Behavioral Research

One of the greatest challenges in Alzheimer's disease research is the translation of knowledge and technology from laboratory and research settings into everyday practical care situations with the goal of improving the quality of life for affected people, their families and care providers. Often, lack of knowledge about what constitutes the most important or "active" ingredient in a successful intervention hinders transporting the technique to usual care settings. There is a huge range of questions in the social and behavioral arenas that are ripe for research. The answers to these questions, if broadly applied, would improve the daily lives of millions of people with Alzheimer's disease and their families.

The Alzheimer's Association has made improving the quality of care for persons with Alzheimer's disease and expanding access to home and community based services top priorities. In addition, we must find ways to support family caregivers who continue to be the backbone of the long-term care system in this country. Seven in ten people with Alzheimer's disease live at home. The estimated annual value of the informal caregiving system is $257 billion, far more than the $32 billion cost of paid home health care and the $92 billion cost of nursing home care. The Association has endorsed several pieces of pending legislation that will help us achieve these goals including:

• S. 566, *the Alzheimer's Disease Research, Prevention, and Care Act of 2003*—cosponsored by the Chair and Ranking Member as well as several Members of this Subcommittee, this bill would reauthorize the highly successful Administration on Aging Alzheimer's Disease Demonstration Grants to the States Program. Thirty-nine States, including both Maryland and Missouri are participating in this unique program that is fostering the development of innovative models of care for persons with Alzheimer's disease and their caregivers, especially those in rural and low-income communities.

• S. 1214, *the Family Caregiver Relief Act of 2003*—sponsored by Senator Mikulski, as well as other Members of this Subcommittee, this bill would provide a $3,000

tax credit to help family caregivers with long-term care expenses such as adult day care and respite care.

• S. 538, *the Lifespan Respite Care Act of 2003*—introduced by Senator Clinton of this subcommittee and co-sponsored by Senators Mikulski, Warner and Murray, this bill would increase the availability of respite care services and provide training for respite care workers and volunteers.

Conclusion

There is now real hope for a future without Alzheimer's disease. Greater understanding of the disease, improved care and treatment, and unprecedented scientific opportunities for delaying onset and preventing the disease can all lead to a future where Alzheimer's is just a memory. Imagine the billions in savings to Medicare and Medicaid if scientists were able to develop a presymptomatic diagnostic technique and a preventive therapy that did not allow the disease to occur. But none of this will happen if we do not take action. Research supported by the National Institutes of Health needs $40 million in additional funding in this fiscal year alone to carry out large scale, controlled, clinical trials that will identify therapies and treatments capable of slowing or halting the onset and progression of Alzheimer's. Basic research has produced breakthroughs in our understanding of Alzheimer's disease, but we need to know whether the discoveries will actually work. Clinical trials are the only way to translate—and verify—the findings of basic research into real-world treatments.

Senator BOND. Thank you very much, Mr. McConnell. I regret to tell you that you come before us at a time of very stretched budgets. Senator Mikulski and I are responsible for funding the veterans' health fund, EPA, National Science Foundation, and the initial numbers we have for those are definitely underfunded, and the National Science Foundation, which I believe supports some of the work at NIH.

Mr. MCCONNELL. That is why we are asking for a modest $40 million increase.

Senator BOND. Well, that is good. I appreciate that. Thank you for that. We would love to be able to fund this and the other things, but we do have a tight budget.

Let me phrase a question just generally. We are very interested on the committee in seeing how we can get quality care for our Nation's elderly. If there is one thing that we can do immediately for the patients and the families who have family members with Alzheimer's—let us start with you, Dr. Hodes—is there one thing we can suggest to a family with a patient with Alzheimer's? What can we do?

Dr. HODES. I think most immediately, as you have heard from Dr. Morris and Dr. Rabins, we have an enormous commitment to educate, while emphasizing at the same time—and I should again repeat our gratitude to Congress for its support and for the enormously effective partnership that Alzheimer's research has had with the Association.

In addition to our long-term goals of finding the ways and means to improve upon our ability to diagnose, treat, and prevent, our most proximal or immediate goal is that of educating and informing. We have to inform the public of the ability to accurately diagnose disease so it can be diagnosed, and we have to inform the public of the opportunities there are to treat, albeit they are still imperfect and temporary solutions which nonetheless do translate in a fraction of individuals to a longer time in touch with their families and loved ones, at home and out of institutional settings.

So this is I think going to be a part of the mission, we appreciate, together with academic institutions and the Alzheimer's Associa-

tion, informing the public about what is available. This is a constant balance we have, to be doing the research now so that 20 years from now, we will have better interventions, hopefully the definitive ones, but at the same time to translate what is now effective into practice by the largest possible community in this country and around the world.

Senator BOND. OK. So the first thing would be if there is a question, get an accurate diagnosis, and then some immediate things can flow from that.

Dr. Morris, would you like to respond?

Dr. MORRIS. I would just augment Dr. Hodes' remarks to emphasize that early recognition can benefit both the patient and the family. Too often, families bring patients in for diagnosis when there is a crisis—someone living alone no longer is safe to live alone, someone driving gets into a car accident, problems with financial mismanagement—all sorts of difficulties that occur in the more moderate or advanced stages of the disease.

Earlier recognition, when patients are still relatively functioning, can allow not only treatments to help maintain that relatively good functioning longer than would occur without the treatment, but it also allows the patient, family, and physician to begin planning for future years to avoid these crises, so driving cessation can occur before there is a crash; assisted living can occur or home health can occur before the individual living alone leaves on the stove burner, forgets to turn it off, starts a fire.

So earlier recognition, earlier treatment, earlier planning to protect assets, to determine who should have durable power of attorney to be in charge of decisionmaking when the individual no longer can do that, I think would go a long way to alleviating some of the very difficult crises that patients and families go through if they wait to get the diagnosis and treatment.

Senator BOND. Thank you.

Dr. Rabins?

Dr. RABINS. I would just build upon those remarks by mentioning that I included in my testimony a study that I have just completed in Maryland, actually, where we looked at a random sample of older people living in the State, and we found that of all the people with Alzheimer's disease, only one-third were known to their doctor to have any problem with memory. So that two-thirds of people with Alzheimer's disease are not even recognized by their doctor.

So the treatments that we do have, the education, the medications, all these early important activities that Dr. Morris mentioned, cannot happen when the doctor has not even noted that there is a problem.

So I think that if we could do one thing, as Dr. Morris said, it would be improving recognition by families and doctors that there is a problem, because then that gets people the help they need earlier.

Senator BOND. Mr. McConnell?

Mr. MCCONNELL. There are simple caregiver supports that can make a huge difference. Respite care is the number one thing that people ask for. Most of the care is being provided by family members, and they do it 24, 36 hours a day, and some respite care, some simple counseling, can make a difference.

There was a recent study that came out of NYU about some simple counseling procedures that appear to reduce depression among caregivers. We funded a study in Cleveland that provided some simple training for caregivers that not only helped them provide better care but significantly reduced emergency room use and unnecessary hospitalization. So there is a cost saving as well as a benefit to the caregivers.

But the problem is that we have those supports, and certainly a tax credit and the Lifespan Respite Care Act can all be very helpful, but people are not getting diagnosed, they are not being told by physicians that there is an Alzheimer's Association that can provide them with information and support, and until we have the medical community better trained and better educated about what is possible, and more knowledgeable about this, people will not get access even to the services that are available now.

Senator BOND. I guess one thing that people need to know is the telltale signs, and I gather that memory loss, forgetting recently learned information, difficulty performing familiar tasks like how to prepare a meal, using a household appliance, and participating in a hobby, problems with language, disorientation in time and place—these are the kinds of things that you look for first, and I assume—there were several references to materials—I gather those are in the materials that the Alzheimer's Association and Dr. Rabins and others have available?

Mr. MCCONNELL. We have something called "The 10 Warning Signs" that we have tried to publicize so the public can ask those questions, or more likely a family member recognizes some of those symptoms and gets a person to a physician to get a diagnosis.

Senator BOND. Thank you.

I will turn it over now to Senator Mikulski.

Senator MIKULSKI. Thank you very much, Mr. Chairman.

I am going to jump around a little bit. Mr. McConnell, how much did you say the Alzheimer's Association spends every year on research?

Mr. MCCONNELL. This year, we will fund about $17 million in research grants, and since our founding in 1980, we have committed $150 million to research.

Senator MIKULSKI. That is really stunning when you think that this was done on Alzheimer's walks and all kinds of very grassroots fundraising. And really, you and all the members of the Association should be complimented on that.

I am going to come back with some ideas on that, but Dr. Hodes, obviously, the doubling of the budget has had a great impact. When I embarked upon this topic 20 years ago, the progression in our family was all the 10 signs that you have indicated, Mr. McConnell, and others began to appear in 1982, and 1984 is when we turned to Dr. John Burton at Hopkins for geriatric evaluation and then went into a specialized day care program that provided 3 mornings a week for Dad; Mother could take a break, and Dad was in these memory stimulation and other groups. In 1986, we had to turn to long-term care, and in 1988, my father passed away.

But every hearing I held was so gloomy and doomy and fatalistic and so on. This has so much energy. This has so much possibility—and also, it is comprehensive, from the family to basic themes like

cholesterol and diabetes management that will have an impact to really enormously sophisticated drugs and genetic therapies.

So it shows that truly, money could make a difference in this case.

Is this right, Dr. Hodes? And Mr. McConnell has talked about $40 million, and Senator Bond is right about the $40 million, but could you tell us what an increase in funding could lead to, or the amplification of a study?

Dr. HODES. To begin with, I can certainly point to how important the doubling just accomplished has been. It has been true at the level of the most stunning, as you characterized them, basic science studies which are really probing at molecular genetic levels the underpinnings of the disease. It is also quite evident in the list that I provided of some of the prevention and treatment trials that are ongoing the fact that we have now opened a number of potential targets which we can, with adequate funding, approach in parallel rather than in sequence is critically important.

The nature of science, and particularly biological investigation, is that we do not know whether it is going to be the trial of statins or of ginkgo biloba or of anti-inflammatories or of the other agents that we are testing, which will be the most effective. And our best opportunity to find an effective treatment or treatments before the crisis is upon us is to be able to pursue these multiple outstanding opportunities created by past and present basic science.

As noted, the increase in budget has now leveled off, and we at NIA and all of NIH will continue, of course, to do our very best to fund the best science at best judgment with this limitation on funding. You have heard some of the numbers expressed, and I can certainly validate what they are.

We have characteristically been able to fund approximately 25 to 30 percent of the most outstanding grants over the past several years. This year, our estimate is that that number will be approximately 15 to 17 percent. And as was alluded to by Steve McConnell, in order to accomplish this, we have actually had to make reductions in those awards that we do make, the alternative being to fund even fewer.

This is not a case where of course we are going to say the most promising studies will not happen. That would be irresponsible, and that is not what we would do. But we would not be able to carry out the number of studies at the pace which is optimal and could be driven by basic discovery.

In that case, simply put, there is now an unprecedented richness of opportunities and proposals.

Senator MIKULSKI. I got it. And I think what I would like to do—and I want to acknowledge what Senator Bond said; it is a tight time—but is to reach out to Senators Specter and Harkin to just say what $40 million would mean, because they have a lot of pondering to do—and we do not want to get into earmarking research, but the idea that this Institute in the scheme of doubling the NIH budget for really, in many ways, a modest increase, the possibilities here, because the consequences again to family and budget and other issues are so enormous. So we will come back to that.

I want to go to, while we are looking for cures and the genetic underpinnings, all of which we want to continue to support, the ability for cognitive stretchout.

Dr. Rabins, could you fill us in or summarize some of the promising ideas? I note that there is a drug called Memantine—how do you say that——

Dr. RABINS. Memantine.

Senator MIKULSKI [CONTINUING]. Memantine—and then also, this whole idea of chelation. What is going on—because the delay of onset would be really enormous.

Dr. RABINS. I think what we know now is that these medicines that we have, at least the way I present it to families, can improve a person by approximately 6 to 9 months. About two-thirds of people have some response to these medicines, so the average person would get somewhat better, but that is a modest improvement.

As far as we know, these medicines do not really slow down the progression of the disease. Some people think that they might, but that has not been demonstrated. So the medicines work, they work very modestly. But that does tell us that it is possible to change what is going on in the brain. I think if nothing else, what we have already tells us that we can change the disease, so we know we can do a lot better.

Senator MIKULSKI. But, Doctor, what slows down? I will wait for a second round to go into chelation and this ginkgo biloba study and so on. But if we say there is modest improvement, but it does not slow down, what is the nature of the improvement?

Dr. RABINS. Well, the improvements seem to be in the area of thinking, so all the thinking problems—and Senator Bond mentioned a number of them—memory, judgment, doing everyday activities—people show improvements in all of those areas, modestly. And second, people do become somewhat more functional, so they are a little bit more able to function in everyday life. They are a little better able to dress themselves, bathe themselves—and although these things do not sound so major, when you are a family care provider——

Senator MIKULSKI. No—they are major.

Dr. RABINS [CONTINUING]. If someone can get dressed when they needed help before, that is a tremendous change.

So it is both in the area of memory and thinking and in the area of everyday functioning that people improve.

Senator MIKULSKI. Thank you.

Senator BOND. Thank you very much, Senator Mikulski.

I am going to ask unanimous consent that a statement by Mr. Eric Hall, CEO of the Alzheimer's Foundation of America, be included in the record as if read. Without objection, it will be.

[The prepared statement of Mr. Hall follows:]

PREPARED STATEMENT OF ERIC HALL

THE ALZHEIMER'S FOUNDATION OF AMERICA

Chairman Bond, Ranking Member Mikulski, and distinguished Subcommittee Members, on behalf of the Alzheimer's Foundation of America (AFA), thank you for holding this important hearing on Alzheimer's disease and recent breakthroughs in medical research. Your leadership on these issues is vital to the success of ongoing work to find a cure for Alzheimer's disease.

I appreciate the opportunity to provide information about AFA members' related efforts to meet the educational, social and emotional needs of individuals with Alzheimer's disease and their families and caregivers, while raising public awareness about the disease and lending expertise to healthcare professionals. I also want to highlight an important initiative launched by AFA to promote memory screening with the goal of early diagnosis of Alzheimer's disease and related dementias.

The Foundation's Mission

The Alzheimer's Foundation of America (AFA) is a nonprofit 501(c)(3) organization founded to fill a gap that existed on the national front for advocacy of "care. . . in addition to cure" for individuals affected by Alzheimer's disease and related dementias. Our goals include improving quality of life for all those affected and raising standards for quality of care.

AFA operates a national resource and referral network with a toll-free hotline, develops and replicates cutting-edge programs, hosts educational conferences and training for caregivers and professionals, provides grants to member organizations for hands-on support services in their local areas, and advocates for funding for social services. It annually sponsors two national initiatives, National Memory Screening Day and National Commemorative Candle Lighting.

Founded in February 2002, AFA now represents organizations in nearly all 50 States. The majority of AFA members provide direct, hands-on educational and social services in their local communities that help individuals and their families cope with this devastating disease. AFA has also established collaborative partnerships with other national groups, including The Leeza Gibbons Memory Foundation, Project Lifesaver and Sunrise Senior Living.

The Importance of Memory Screening

AFA launched National Memory Screening Day in 2003 as a collaborative effort by organizations and health care professionals across the country to promote awareness and early detection of memory impairments. AFA initiated this effort in direct response to breakthroughs in Alzheimer's research that shows the benefits of early medical treatment for individuals with Alzheimer's disease, as well as the benefits of counseling and other support services for their caregivers. AFA's National Memory Screening Day underscores the importance of early diagnosis, so that individuals can obtain proper medical treatment, social services and other resources related to their condition. With no cure currently available for Alzheimer's disease, it is essential to provide individuals with these types of interventions that can improve their quality of life while suffering with the disease.

During National Memory Screening Day, healthcare professionals administer free memory screenings at hundreds of sites throughout the United States. A memory screening is used as an indicator of whether a person might benefit from more extensive testing to determine whether a memory and/or cognitive impairment may exist. While a memory screening is helpful in identifying people who can benefit from medical attention, it is not used to diagnose any illness and in no way replaces examination by a qualified physician.

The benefits of an early diagnosis of a memory disorder are enormous. Early diagnosis can go a long way toward improving quality of life. National Memory Screening Day represents a giant step toward leading individuals up the right path.

Our goal is for individuals to follow up with the next steps—further medical testing and consultation with a physician, if the testing raises concerns. The latest research shows that several medications can slow the symptoms of Alzheimer's disease and that individuals begin to benefit most when they are taken in the early stages of memory disorder. This intervention may extend the time that patients can be cared for at home, thereby dramatically reducing the costs of institutional care.

With early diagnosis, patients and their families can also take advantage of support services, such as those offered by AFA member organizations, which can lighten the burden of the disease. According to several research studies, such care and support can reduce caregiver depression and other health problems, and delay institutionalization of their loved one—again reducing the economic burden of this disease on society.

In addition, with early diagnosis, individuals can participate in their care by letting family members and caregivers know their wishes. Thus, memory screenings are an important tool to empower people with knowledge and support. Just as importantly, the screenings should help allay fears of those who do not have a problem.

AFA holds National Memory Screening Day on the 3rd Tuesday of November in recognition of National Alzheimer's Disease Month. AFA sponsors it in collaboration with The Leeza Gibbons Memory Foundation. Ms. Gibbons founded The Leeza Gib-

bons Memory Foundation in response to her own family's trial with Alzheimer's. She lost her grandmother to the disease, and her mother now battles with the final stages of Alzheimer's.

This year, National Memory Screening Day will be held on November 16, 2004. Individuals concerned about memory problems will be able to take advantage of free, confidential screenings at hundreds of sites across the country with the goal of early diagnosis of Alzheimer's disease or related dementias. Early diagnosis is critical, because as Ms. Gibbons has noted, "This is not a disease that will wait for you to be ready."

The Need for Federal Leadership

As promising research continues in the search for a cure, additional resources are also needed in support of efforts to delay the progression of Alzheimer's disease and related dementias. The Federal Government can play a critical role in that regard by providing resources for a public health campaign designed to increase awareness of the importance of memory screening and to promote screening initiatives.

Federal support is essential to expand the scope of ongoing efforts in the private sector. Working in partnership with AFA and other participating organizations, the Federal Government can leverage its resources cost-effectively to help overcome fear and misunderstanding about Alzheimer's disease and related dementias, to promote public awareness of the importance of memory screening, to expand options for screening nationwide, and to direct Americans to the support services and care available in their local communities.

AFA appreciates the subcommittee's leadership on these issues and welcomes the opportunity to work together to improve the quality of life for Alzheimer's patients, their families and caregivers. (322 8th Ave., 6th Fl, New York, NY 10001, Tel 866–232–8484, Fax 646–638–1546). (www.alzfdn.org).

Senator BOND. I would like to turn to Dr. Morris. We heard earlier about the imaging and the clinical trials. Can you give us an idea why imaging is so important in clinical trials?

Dr. MORRIS. Yes, thank you.

Let me begin by indicating now that the treatments that Dr. Rabins just discussed help people modestly. A reason for that is that we initiate treatments when we diagnose the disease. We diagnose the disease when dementia occurs—memory loss, other problems. By the time memory loss has occurred, we know already that there is substantial brain damage. In some vulnerable areas of the brain, already 60 percent of nerve cells have died by the time the diagnosis is made. In some sense, if we wait until dementia appears so that we can make the diagnosis, it is too late to have any major therapeutic effect. The brain is already substantively damaged. Hence, in order to optimize treatment, we have to recognize the illness at stages before that substantial brain damage occurs, when it is just beginning in the brain.

Dr. Hodes mentioned this very exciting imaging study where we can now introduce a tracer into the bloodstream of a patient, it gets into the brain, and it attaches to the beginning brain changes of Alzheimer's disease at a stage before many nerve cells are lost.

So the value of imaging is early detection, detection before the stage of dementia, and will give us an opportunity to evaluate interventions to fix that abnormal brain stage. So we can not only use imaging as a potential tool for presymptomatic recognition of the disease before substantial brain damage has occurred, but also monitor the effective treatments that attack the actual underpinnings of the disease—not the symptoms, but the causes that result in nerve cell death.

What we are talking about is prevention of Alzheimer's disease.

Senator BOND. Normally, what would you say are the symptoms, what are the indicators that would merit such an intervention? If

you tell me that half of 85-year-olds have Alzheimer's disease, it would seem to me that 100 percent testing when you are going to get 50 percent hits would make sense. What would be either the age or the early indicators before the loss of brain cells occurs that would warrant widespread use of these tests?

Dr. MORRIS. Well, that is an excellent point, because we cannot do a brain image in every 60-year-old or 50-year-old. It is just too expensive and too difficult. So we have to narrow it down to people who already seem to be at increased risk.

One way that there is increased risk is we know that if there is a family member—a parent or a brother or a sister—with the disease, the genetic inheritance puts individuals at greater risk.

Hence, I think we need to look at these high-risk individuals to see if they are beginning to develop the illness, and when we get these new interventions that attack the disease process, that is the target group for the interventions, rather than to give it to everybody.

Senator BOND. Would things like diabetes and high blood pressure be indicators as well, so that diabetics should be included, or is that too broad a category?

Dr. MORRIS. Actually, I think there are many possible risk factors. Diabetes is one. But I would say that we can do even better than just broad risk factors. I think we can look at individuals who are specifically at risk for Alzheimer's disease.

There is no question that anything that damages the heart—high blood pressure, high cholesterol, diabetes—is bad for the brain. There is no question about that. But we are talking about specific causes of Alzheimer's disease, and we can look at the specific risk factors for that.

Dr. RABINS. Could I add something to that, Senator?

Senator BOND. Sure.

Dr. RABINS. You are actually thinking like a scientist, and all the questions you are asking are the kinds of questions that a scientist would ask. And only with study will we know that there is a given age at which it is worth doing, or particular conditions. So it is those kinds of studies that will build upon this imaging initiative that will answer the kinds of important questions you are asking.

Senator BOND. Dr. Hodes?

Dr. HODES. I think we all have the same thought, that we probably ought to recruit you to some of our study sections, because you are really asking precisely the correct questions.

But as examples of some of the instances in which imaging abnormalities have been seen in populations at high risk and may begin to answer the question that you have posed, they include studies that have been done on individuals with genetic high risk of disease—either carrying the APOE allyl or even in early onset—and are quite striking, and it remains to be seen what the final implications will be of these studies. In individuals with APOE-4, a risk factor for increased likelihood of Alzheimer's disease, it has been shown that individuals in their middle years, and most recently in one report, even in their twenties and thirties, begin to show some of the brain changes in imaging that are characteristic of patients with Alzheimer's. This is a clue that some of the early changes may be detectable in a population that is at genetic high

risk and begins to address the very important questions that you are asking—what are the populations that we should target for this kind of diagnostic intervention, and from a research point of view, which of the populations we should target for experimental treatments to prevent progression of disease.

Senator BOND. Thank you.

My apologies to my colleagues. Just one last question—and I might ask if Mr. McConnell has anything he wants to add on that.

Mr. MCCONNELL. There is a question right now about whether this PET scan technology which is getting a huge amount of attention should be covered by Medicare, and the general sense is that it is not ready in a general population for that purpose, but as a research tool, it is very important, and I think there is huge hope for imaging being both a diagnostic tool and to help move treatments more quickly to the market.

But we do not support broad-scale screening, because you can create mass hysteria out there. A lot of us are worried about our memories, and I think it is important that we target those people right now who are showing some significant deficit and not try to scare the whole population by massive screening.

Senator BOND. One final thought—you are telling us it is cardiovascular, it is blood-related, and you talked about elements in the brain. Do any of these show up—because almost all of us from time to time should be having blood tests to check our cholesterol that would indicate the need for imaging?

Dr. HODES. I think any of the experts here can address this question, but the short answer to your question is that there certainly are risk factors determined by blood tests which identify individuals at a higher risk. These include such things as high cholesterol or high homocysteine levels.

What remains as an important link is to prove that treatment of those risk factors will actually affect the risk of disease, and those are studies ongoing. So if one affects cholesterol with drugs like statin, which has many effects, or with folic acid, which can reduce homocysteine, the clinical studies now in progress will help to identify whether these are risk factors which when modified will actually translate into a prevention or slowing of disease.

Senator BOND. Thank you very much.

We have been joined by the senior Senator from Connecticut.

Senator Dodd, would you care to make a statement or ask some questions?

OPENING STATEMENT OF SENATOR DODD

Senator DODD. Thank you, Mr. Chairman, and I apologize for arriving a few minutes late.

Let me thank you and Senator Mikulski for holding this hearing. I think it is tremendously worthwhile. I represent a small State of 3.5 million people, and 470,000 of my constituents are older Americans, and 100,000 of those 470,000 are at one stage or another of Alzheimer's disease. I think our State ranks ninth in the country because we have an older population.

I also wonder whether there are environmental implications to all of this—you may have talked about this before I arrived—in addition to the lifestyle issues.

As a layman—and I am talking to a panel of professionals—but watching what appears to be—maybe it is because there is better detection available today—but what seems to be an increase in the number of diseases, I am wondering if there are more environmental implications than we are willing to admit or look at that are provoking some of this increase in a number of related areas, Alzheimer's being one of them. I wonder if you might talk about that.

Second, you may have addressed this already, and I know this is a subject of some controversy, but I want to express my admiration for Nancy Reagan and her comments the other day before the Juvenile Diabetes dinner in Los Angeles. I spoke at the dinner for the Northeastern Conference. I am very involved, and I have a godchild with juvenile diabetes, and every year, I am very much involved in their efforts in Connecticut and western Massachusetts. Obviously, the stem cell issue is an emotional one for a lot of people, but clearly, when you start talking about juvenile diabetes and Alzheimer's and Parkinson's disease and others, being able to access, particularly as there is an effort now with the frozen embryos that may be discarded shortly, it would be a great pity in my view if we did not take advantage of that existence to utilize the efforts that are being made to try to come up with ways to effectively deal with Alzheimer's.

So I would like to ask the panel if you have not already addressed these questions about, one, the environmental issues generally speaking—and I realize it is a broad question, and again, I realize the question is coming from a layman, but nonetheless I have the feeling and sense that more is going on here than we are really willing even to admit at this juncture—and second, I wonder if all four of you would comment on the embryonic stem cell issue.

Dr. RABINS. I think as far as environment and the large increase in the number of people with Alzheimer's disease, as far as we can tell—and the research only goes back about 50 years—the percentage of people who develop Alzheimer's disease at any given age is not increasing. What has changed is that for the first time in human history, it is common for people to live into their seventies and eighties. The average woman now in the United States lives to age 80. So if somewhere between 20 and 35 percent of 80-year-olds have Alzheimer's disease, that is a huge number. Again, the average woman lives to 80, so that means the average woman has between a 20 and 35 percent chance of getting the disease.

So the reason we are hearing so much about it is because of this change in the way the population is distributed. There are many more older people at risk.

My own personal opinion about stem cells is that it is very difficult to predict whether they could be beneficial in Alzheimer's disease. We will obviously never know unless that kind of research goes on. I think the opportunity if they were to help would be very, very early in the disease—if we could find that there were a focus of cell death that triggered the disease and possibly reverse that. But it is a disease that ultimately envelopes almost the whole brain, so it is hard to see—although one never can tell—how stem cell research might influence the disease. That is my personal opinion.

Senator BOND. Dr. Morris?

Dr. MORRIS. I would just like to echo Peter's comments about the real influence of the aging of the society as the major driver for the increased recognition of Alzheimer's disease. I think by far and away, it is this demographic revolution that makes us have this epidemic before us.

But it is interesting that all of those things that we have heard about, about keeping good health, good cardiovascular health, physical health, mental health—the things that Steve McConnell talked about—are really excellent. As a matter of fact, Steve talked about dancing, but it is known that staying mentally engaged is actually associated with some decreased risk of developing Alzheimer's disease, and one of the major factors I think is testifying before a Senate subcommittee; I think that is very protective.

Senator DODD. Hopefully those who are up here are remembering what you are saying to us.

Dr. MORRIS. And I would just like to mention one thing about Nancy Reagan, not on the stem cell issue. I think too many people still have a stigma, a negative stigma, attached to Alzheimer's disease. It is one of the barriers for coming forward for early recognition. And I think President and Nancy Reagan's statement that he did have Alzheimer's disease several years ago was very courageous and went a long way toward reducing that stigma.

Mr. MCCONNELL. Senator, if I could pick up on that, I think one of the things that is happening is that people are being diagnosed earlier. So in addition to the longevity question, you have more people with the disease, more people are being diagnosed earlier, and we are finding that the conversations that happen at any meeting of the Alzheimer's Association have shifted, because there are present always people with the disease. They speak, they represent themselves, they feel strongly about these issues, and it has changed the conversation.

I think it contributes to that sense that there is an epidemic, and it is an epidemic in the sense that it is growing in huge numbers and having huge impact. It just is not the same kind of epidemic.

Senator DODD. Do you want to comment on the stem cell issue?

Mr. MCCONNELL. We took a position against the Federal ban. We have tended to focus on other areas of promising research to lend our support, and as you have just heard, there are questions in the science community about this issue, but we felt that there should not be a Federal ban against stem cell research, because there may be some opportunities to explore understanding of how they work.

Senator DODD. Dr. Morris, did you want to comment on that as well, stem cells?

Dr. MORRIS. I would have to say specifically for Alzheimer's disease that I think stem cell research is not likely to have an immediate impact. There are other neurologic diseases such as Parkinson's disease which affect a very discrete area of the brain for which the potential therapeutic impact of stem cell research I think will have much more immediacy than for Alzheimer's disease.

So from a scientific standpoint, I think brain diseases, in particular those that affect only a local, discrete area of the brain, will potentially benefit more from stem cell research. Perhaps down the road, Alzheimer's disease may benefit also.

Senator DODD. Can I glean from that, then, that you would be opposed to a total ban on the stem cell research?

Dr. MORRIS. Well, I have to tell you I am a scientist, so as a scientist, we like to be able to follow promising leads wherever they go.

Senator DODD. Thank you.

Dr. Hodes?

Dr. HODES. In terms of the question of risk factors and environment, I would certainly reinforce what you have heard. Such issues as life style risk factors are part of environment. But Senator Dodd, you make an important point I think all of us would agree upon. We have to have appropriate humility about what we know and what we do not know, and I would stress that we are constantly looking in studies of the epidemiology and risk factors for any possible environmental or other factors which may play a role which we do not yet appreciate. I think we would all reinforce that most strongly.

Senator DODD. And on the stem cell issue?

Dr. HODES. In terms of stem cells, again I would emphasize that there is a broad spectrum of stem cell research that is being carried out in brain research, in Alzheimer's research in particular. It includes embryonic stem cells, adult stem cells, the demonstrated ability of cells within the brain itself to be potentially mobilized with differentiation.

Clearly, our responsibility at the National Institutes of Health is to support all of that research which is consistent with policy set by the Federal Government.

Senator DODD. Thank you all very much.

Mr. Chairman, thank you. I would note just in closing that years ago, when I first got involved, it was because of Yasmine Kahn's mother who had begun to talk about it. And in fact, Sil Conte, one of the early Members of Congress in the House really got involved in this issue.

So we have come a long way, and I thank you very much.

Thank you, Mr. Chairman.

Senator BOND. Thank you very much, Senator Dodd.

Senator Mikulski?

Senator MIKULSKI. Thank you, Mr. Chairman.

While we are talking about breakthroughs, I am going to return to the conversation of the more ordinary that came up. What I found so interesting were the issues about Motrin and Advil, issues of possible vitamin intervention, all of which is good health, the role that diabetes and cardiovascular is playing and the telltale signs.

So, Dr. Rabins, in your newsletter, the Hopkins newsletter, you talk about the concept of metal chelation. I believe in the Archives of Neurology, you reported that there was a drug that worked on the chelation idea. Could you elaborate on that? We know that in lead paint poisoning, chelation really helped restore the cognitive ability of children, and you know that our City of Baltimore is one of the lead paint areas. Could you tell us what that means, and does this offer some promise to this, and is this something that should be explored more readily?

Dr. RABINS. I think it is certainly something that should be explored. As we study the biology of these proteins that are being deposited in the brains of people with Alzheimer's disease, we are discovering all kinds of unsuspected things, and one of those is the fact that within these clumps of protein, there are these metal ions that are part of the deposition of these proteins. So, theoretically, it might be possible if one could remove some of those metallic ions that one might actually be able to remove some of the proteins that are being deposited.

I think this preliminary study is very preliminary, and whether we can really change the course of the illness I think has not yet been demonstrated. But it is one of so many leads that we really need to study in a proper way.

Senator MIKULSKI. And it is really a technique that has now been around for a while because of the issues like in lead paint; am I correct?

Dr. RABINS. That is true. One needs to find particular medications for each different ion, so the question would be specifically what is happening in Alzheimer's disease, and are there drugs that can remove these ions, and then, does that really make a difference regarding disease progression. So it is an open question.

Senator MIKULSKI. Dr. Hodes, and then I want to go to the vitamin approach and hear from the Center on Complementary Medicine about their ginkgo research.

Dr. HODES. Senator Mikulski, I was precisely going to suggest that the area of chelation, in addition to the topics you mentioned, Dr. Straus can speak to clinical studies that are currently ongoing.

Senator MIKULSKI. Dr. Straus, maybe you could come up.

Gentlemen, colleagues, this is Dr. Peter Straus, who is at the National Center for Complementary Medicine at NIH. Senator Harkin has been the prime mover in establishing this Center, and I supported him for two reasons. One, we wanted to be sure that as the whole information of complementary medicine exploded, the American people were prevented from quackery, to make sure they were not just on a fool's journey or even being victimized, and at the same time, lessons learned from other countries, particularly England, which uses complementary medicine, from acupuncture to botanical remedies and so on.

Dr. Straus, it is good to see you. We have heard a lot about this ginkgo research, and you talked about stigma. There is a lot to joke about it, but you know, this is where our public is. You can pick up any vitamin book, and it says take this, and you do not have to take that; or this is going to lower your blood pressure and revitalize your relationship with your spouse, and all that.

So people are doing it. The question is how can we ensure that we prevent them from going on a fool's journey and at the same time maybe embark upon a journey that is a breakthrough?

Senator BOND. Before you start, I would say I hope it is not a total dead end, because I planted ginkgo trees along with my nut trees in Missouri.

Dr. STRAUS. Mr. Chairman, Senator Mikulski, Senator Dodd, it is a pleasure to join my distinguished colleagues. As part of the NIH doubling, our Center was created at the NIH, and our purpose is to really help inform the public and practitioners about things

that we may choose to do today, wise or not, while waiting for the genetic and diagnostic and biological and therapeutic interventions to come from our research laboratories.

About half of my budget goes to aging-related research, because over one-quarter of Americans over age 60 are moving to use dietary supplements and various manipulative and exercise approaches and meditative approaches. These are hugely important.

We are supporting in partnership with the Aging Institute a number of studies of antioxidant vitamins, micronutrients, the vitamin E and selenium study and the like. But I take particular pride in the studies that we have been doing with ginkgo biloba.

As Dr. Hodes mentioned in his testimony, this is the largest study ever done of herbal medicine. There are 3,073 patients, otherwise healthy Americans, age 75 and up, who have volunteered for a multicenter trial around the country. And we are asking whether the kinds of preliminary observations that emerged from Europe with ginkgo biloba were correct, whether it can prevent cognitive decline.

To do a study like this and to do it right, to do justice to the over 3,000 volunteers for this study, requires all of the imaging and neurocognitive testing tools that we can bring to bear to diagnose the disorder, and that is what we are doing.

We had believed initially that this study could be done with 2,000 patients. We had to enlarge it, and we will have to extend the study because the rate of——

Senator MIKULSKI. Dr. Straus, where are you in this study? Are you just starting it, and what do you know about it already?

Dr. STRAUS [CONTINUING]. Senator, what we know is the following. This study is fully enrolled for the past year and a half. The rate of Alzheimer's events is less than we had predicted. We will have to extend this study longer to get its endpoint.

But what we do know is that safety is always a concern with these agents, and we are tracking the patients carefully, and thus far there are no safety concerns whatsoever.

Senator MIKULSKI. And what about the issues that others have talked about related to the antioxidants—you used those technical terms, but we know them out in the neighborhoods and communities as B12 and so on, vitamin E—because again, and I want my colleagues to know, we are using the standard Western medicine clinical methodologies—but Dr. Hodes, and maybe you want to elaborate on this, because these again go to the lifestyle issues that Mr. McConnell was talking about, and all of this in terms of things that can be used.

Dr. HODES. The general statement I think it is important to make is that we have a real responsibility in trying to weigh the potential gain versus potential risk of any intervention—and interventions include such things as vitamins, so we do need to take great care.

We have identified, as mentioned previously, risk factors such as, one example, homocysteine, that can be elevated as a risk factor and can be reduced by folic acid. Although there has been no proof, I should stress, that that will decrease the risk of Alzheimer's disease, the question is whether folic acid can be taken safely so there

is little reason not to do it, or whether we need to be more careful of that.

I think in the case of folic acid, in particular with dietary supplements, the decision has been made. Individuals are being exposed to folic acid. The folic acid content in a multivitamin has been so widely used there is little chance of it having an adverse effect.

But I should point to examples where we have been sadly surprised in the past, such as high doses of antioxidant vitamins to prevent lung cancer in a study reported a number of years ago in a population of smokers. That study was stopped because there was, to everyone's surprise, an increase in the risk of lung cancer in individuals taking those vitamins.

So I want to stress that the reason for carrying out careful studies, even if things that are called dietary supplements, can be critical both to identify what is effective but also to prevent terrible and tragic mistakes by taking treatments on the notion they could cause no harm when in fact the potential for harm is there.

Therefore, as we have pointed out, for vitamin B, folic acid, vitamin E, these are all part of past and present rigorous clinical studies in which we will have the answers but do not yet, and until that time, I think we cannot in conscience make an evidence science-based recommendation about widespread use of materials that have not yet been shown to be without toxicity.

Senator MIKULSKI. I see my time is up. I want to come back to Dr. Rabins' newsletter again, "Health After 50." One thing it also talked about, while it talked about promising work in Alzheimer's, it says, "Your dietary arsenal against eight serious disorders," and these are essentially tips for anyone who is looking for nutrition, exercise, etc. It goes through the kinds of programs you should follow if you have a propensity to diabetes and so on. After it goes through all that, it then says "Action Steps," and it says to rely mostly on diet, that the best place to get vitamins is not out of a pill bottle but from a produce store. Then you go into "Color Counts"—get enough vitamins C and E, and so on. I felt like Wonder Woman just reading it.

But this takes me to another issue which is really the subject of another hearing, and that is that most doctors do not know about nutrition. There is so much confusing nutrition advice just as there is confusing vitamin research, gentlemen. There is so much confusion—should you be on "sugarbusters"? Should you be on low-carb? Should you be on low-fat? Should you, should you, should you? America is really confused, and as a result, we are pursuing one fad after another—and maybe some of it has validity. We do not know that.

What we also find, though, is that most physicians really do not offer advice. You get a little piece of paper that says why don't you follow this and so on. That is not a criticism of them. They are under tremendous stress. But I think we are going to have to also look at what goes on in clinical practice with very practical things in addition to very important drugs and surgical interventions.

So I am not opposed to it, but everything that you have said here is that one of the best ways to begin to deal with this in yourself—you might not be able to beat genes, but you can delay the onset.

And if you are managing your life in terms of other propensities you might have, you are also managing this.

I think this is a subject of another whole hearing and discussion, but I want my friends at Hopkins to know that I really do read the newsletter.

Dr. RABINS. Thank you, Senator.

Senator MIKULSKI. I want to thank everybody, though, for all the work that you are doing, and we are so pleased that the complementary medicine is now integrated into sound research.

Thank you, Dr. Straus. We could talk all day about this, but thank you.

Senator BOND. Thank you, Senator Mikulski.

I guess I will just get on your mailing list for the newsletter.

Dr. RABINS. I will make sure you are, Senator Bond.

Senator BOND. Thank you.

I am on the Atkins diet, and it has kept the weight off me for a year and a half, so I hope the studies do not show it was a mistake.

Let me come back generally to the subject at hand. Dr. Hodes, you mentioned the National Institute on Aging's REACH Project, that nine different social and behavioral interventions were tested for enhancing family caregiving. What were some of the more effective ones, and which interventions would you be including and combining in the second phase of your study?

Dr. HODES. The first stage was really a pilot that tested multiple interventions and multiple combinations in relatively small numbers, and I think the most rigorous answer is that none of the interventions actually achieved individually sufficient significance to be making recommendations on that basis.

What this pilot study did, which is often the case with preliminary studies, is to suggest what might be most promising and combine them in a second stage, which is the study now in progress, that has more power in terms of numbers and specific protocols to provide an answer. We are about 2 years into that study, and my expectation is it will be 2 to 3 years more before we have the final answer that could potentially be translated into actual clinical recommendations.

Senator BOND. Can you give us an idea of some of the things that are in this second-phase study?

Dr. HODES. They include such things are providing respite care, using World Wide Web and electronic access, networking—multiple approaches that are designed to ease the burden and make it easier for caregivers to maintain loved ones in a noninstitutional setting.

Senator BOND. I have been a long-time advocate of respite care for family members who are caregivers for adults with any kind of problem requiring assistance. I think that and in-home health care are extremely important and too often shortchanged in Medicare reimbursement. A few years ago, the unwise overreaching cuts in Medicare reimbursement for in-home health care shut down one-third of the home health agencies in my State, particularly in the rural areas, with devastating impact. That kind of care is so critically important, and we will continue to fight and to work on it.

Mr. McConnell, just for the record, you might give us just a few of your ideas on the challenges faced by Alzheimer's caregivers, and what are some of the key factors that you see making caregiving for an AD patient so difficult?

Mr. MCCONNELL. If we break this up into people providing care in the community, the family caregivers and so forth, it is the constant stress. This is a disease where you have to keep track of somebody, and as Senator Mikulski knows, it is enormously stressful for caregivers and families. Many of these caregivers are themselves elderly, so they have their own conditions that they are dealing with; in many cases, they are frail and have their own health problems. The pressure of being a caregiver simply adds to those.

And as you point out, by looking at just the long-term care side of this, we miss the fact that these are people who are using the health care system, and they are using Medicare, and the Medicare system is not set up to deal with people with chronic conditions, with Alzheimer's disease.

Our research shows that Medicare spends three times as much if Alzheimer's is present with other chronic conditions, because Alzheimer's complicates the care; it is much more difficult to care for somebody.

So those are the challenges. We have to make the health care system work better. We have to provide support for families. But I do want to mention that there are people, mostly in the later stages of the disease, who end up in an institution. And we talk about that nobody wants to be in a nursing home and so forth, but the fact of the matter is people need that kind of care when the family can no longer provide it, and many families keep caring for people too long. And we need to be sure that there is good quality care in those settings as well, and we have actually learned a fair amount about how to do that; we just need to get it implemented.

Senator BOND. It seems to me that whenever I am home, the newspaper or the radio will report a tragic circumstance where an elderly person has disappeared, and sometimes it is from a good institution or an institution that thinks it is able to handle the patients, and they have just enough ability to slip out, or the tragic one is where the family is trying to give care, and it may be the middle of winter, and the AD patient goes out for a walk and never comes back.

Mr. MCCONNELL. The Alzheimer's Association has a Safe Return Program. It is a bracelet registry, so that if somebody wanders, the family can call an 800 number in Chicago, and immediately, emergency personnel are notified so they can look for this person. Police departments love this program because they struggle with these issues. If they find somebody with dementia, they do not know how to return them, or it costs a lot of money. If they have a bracelet, they can call an 800 number when they find the person and return them home safely. It has been a very effective program.

We are now looking at some of the new technologies, GPS and cell phone technology, that may be able to track people so that when they wander, you can find out right where that person is at any given time and retrieve them. This could be helpful.

Senator BOND. You hate to think of using a GPS locator, normally a great invasion, but that might be the life saver for an Alz-

heimer's patient if that bracelet had a GPS chip that could be activated or was active. That is an interesting idea.

I turn it back to Senator Mikulski.

Dr. RABINS. Senator, if I may, could I add one thing?

Senator BOND. Please.

Dr. RABINS. It is about stress on caregiving. One thing that I think is often not appreciated is that about 60 percent of Alzheimer's patients have what has traditionally been called a psychiatric or behavioral symptom, and I think, as has already been mentioned, the greatest predictor of ending up in a nursing home is having Alzheimer's disease.

If you have Alzheimer's disease, in fact, the greatest single predictor of going into a nursing home is having a behavioral symptom. So not only are there the physical burdens of caring for a very ill person, but many of these individuals have delusions, they think things to be true that are not true so they make accusations; they are fearful, afraid they may be poisoned; they hear things or see things that are not there; or they become depressed, and that further makes the disease worse.

What is important about that is that in fact those symptoms often can be treated even when the disease itself cannot be changed. So one of the things that we have to help caregivers understand is that there are certain target symptoms that sometimes we can make a difference with, and hopefully, that will then improve the caregiver's quality of life.

Senator BOND. Thank you very much.

Senator Mikulski?

Senator MIKULSKI. I think those comments were very insightful. From what we hear in the community, when the person with Alzheimer's begins to learn the ability to tell night from day, the so-called time reversal—waking up at 3 in the morning thinking it is 3 in the afternoon and wanting to live that way—the caregiver just starts to wear out, and then the children of the caregiver and the Alzheimer's family just get so frustrated and then move on to long-term care.

This is where there is no real reimbursement for specialized day care—and I am not talking about babysitting here, I am talking about the kind that really offers "maintain your brain" activity, supervises medications for other situations, but also provides a breather.

So I think we need to look at care in a continuum from prevention to early diagnosis to intermediate care—not only assisted living, but essentially assistance with living—and that is what some of these do.

Mr. McConnell, can we come back to this idea of the Maintain Your Brain Campaign, which is really a robust grassroots effort, and could you tell us what that is composed of and essentially where did you get your ideas? Was it from the other research and so on?

Mr. MCCONNELL. Yes. There are a couple of things. I mentioned this brochure, and we are trying to get the word out, and it really comes from the scientists. We are very closely tied to the science community—we do not do things unless there is enough scientific evidence to support it—and we feel that there is. So there is a mes-

sage that we can put out there, but getting the message out is part of the challenge.

We created something called the Coalition of Hope. It is 150 organizations now, from The Grange to minority groups; The Urban League is a part of this. It represents 50 million people, and these organizations are kind of the "unusual suspects," we call them—they are not the ones that you ordinarily expect are going to care about this—but they are finding in their membership that they are confronting Alzheimer's disease—either their members have it or parents of their members have it—so they signed onto this Coalition of Hope to try to help us bring an end to this disease and make sure that there is support out there.

Senator MIKULSKI. What are some of the tips that you give people?

Mr. MCCONNELL. The tips, as I mentioned, are to watch your numbers, to manage your cholesterol and your weight and so forth. There are vitamins that we think are useful to be sure your diet is good, and exercise.

But some of it is to increase awareness. For example, in a week or so, we are going to release a report on the impact of Alzheimer's disease in the Hispanic community. There is not a lot of awareness out there in that community. We have not done a good job of reaching out. So we have to create awareness. Once there is some awareness, then people can be receptive to the messages about what they can do, and that is what our efforts are in Maintain Your Brain. Maintain Your Brain is a different message than has gone out there before. As you point out, this is a hopeful message. This is not depressing. There are actually things that can be done, and we think it will open people's minds up to dealing with this issue, whereas in the past, the curtain just came down when they heard "Alzheimer's disease."

Senator MIKULSKI. What I find so interesting here is that when you go to page 2, it does talk about follow the numbers, feed your brain, etc, but there is also the issue that in certain ethnic groups, there seems to be a propensity toward certain risk factors. African American men are well-known for high blood pressure. There is the so-called barbershop outreach, where you get a haircut, and your blood pressure is taken, and we know in our own community that lives have actually been saved that way. Among Native American women and, again, African American women and Latino women, there seems to be a propensity toward Type 2 diabetes. This is a big deal because of consequences generally to health care and so on.

Are you really focusing, then, through these practical things—because when you go around to the churches and community groups, you do not hear this kind of talk. You hear about access to health care—you hear about that a lot—and of course, access to jobs. Those are the two things that I hear. But then, there are the consequences. So how are you linking up to these communities?

Mr. MCCONNELL. As I said, the Coalition of Hope is a good start, because there are a number of organizations that have signed up for that that are saying exactly what you said, that we recognize these larger health problems, but the issue of Alzheimer's disease is something that we have not focused on.

So we are trying to get information out, summarize the research on this, make sure there is better research showing the differences among ethnic groups. But it is a challenge. I think, exactly as you said, we need to go out through churches, through community groups—we need to stand at the WalMarts and get this message out there, which is what we are doing through our chapter network, to increase awareness, let people know there is something they can do and to engage them in dealing with this issue.

Senator MIKULSKI. Well, this has been a wonderful hearing, Senator Bond. Thank you for providing the leadership for us to organize it.

Each and everyone of you just offered such excellent ideas and hope, and it shows very clearly that our responsibility is to create the framework so these ideas can be explored.

We could spend all day with each and every one of you, but you have your research and clinical practice to do, so we want to thank you. We particularly also want to thank the Alzheimer's Association. What a great, strong grassroots organization, and they just will not give up, and we are going to find those breakthroughs.

So I want to thank you all for appearing today. You have given us a lot of things that we need to ponder and also some fiscal directions that we need to be looking at.

Thank you.

Senator BOND. Thank you, Senator Mikulski.

It will challenge our minds to grasp the significance and the breadth of this problem. I had known about Alzheimer's anecdotally and through special areas where we have had problems, as I have mentioned, with providing the right kind of care in my State. But when you tell me that 85-year-olds have a 50 percent chance of having Alzheimer's, that is something that we have to take seriously, and yet I think you have shown us that there are some promising avenues for us to pursue, and Senator Mikulski and I do not directly control it, but I think you can count on us being very strong supporters of the—what was it—you have squeezed it down to, what, $43 million?

Mr. MCCONNELL. Just a mere $40 million.

Senator BOND. Just a mere $40 million, okay.

Mr. MCCONNELL. That is chump change up here, really, and it could do a huge amount.

Senator BOND. Well, I know. Unfortunately, it is clear that there is some tremendous potential ahead, and we will not treat it as chump change. We will treat it and hope that our colleagues on the Labor-HHS Appropriations Subcommittee can find it.

I really congratulate you, all the people with whom you work, and the organizations you represent, for your significant contributions.

Dr. Straus, thank you very much for being here. I will have to check on some of the alternative medicines that I am taking after the hearing is over.

With that, the hearing is adjourned.

Thank you.

[Additional material follows.]

ADDITIONAL MATERIAL

ACADEMY OF MOLECULAR IMAGING

Chairman Bond, Senator Mikulski and Members of the Subcommittee, I appreciate the opportunity to submit testimony on recent breakthroughs in Alzheimer's disease research and the importance of developments in molecular imaging for the early and accurate diagnosis and evaluation of Alzheimer's disease (AD) and related dementias. On behalf of the Academy of Molecular Imaging and of professionals involved in clinical care and research devoted to the welfare of patients with Alzheimer's disease and related dementias, we deeply appreciate the subcommittee's interest and scrutiny of the changes in scientific and clinical practice which promise to improve the outcomes and the quality of care for Alzheimer's and patients with other forms of dementia.

As a health professional, it has been extremely exciting for me to observe and participate in the recent progress made in developing PET scans as a diagnostic and evaluative tool for these important diseases and disorders. Dementia is the most common cause of mental impairment in older persons, affecting 8 percent of those age 65 years and older and up to 47 percent of those in the age group 85 and above.

Alzheimer's disease is the most common cause of late-life dementia, accounting for nearly 70 percent of cases. Other relatively common causes include vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and depression.

Importance of PET Scans for Dementia

PET scans, using 2-deoxy-2-[F–18] fluoro-D-glucose (FDG), provide measures of glucose metabolism that allow clinicians to make an early diagnosis of AD and other neurodegenerative disorders, predicting clinical progression and the autopsy diagnosis with superior sensitivity and accuracy, especially in the earliest stages of dementia when clinical impressions are least certain. PET determinations of glucose metabolism in AD show a specific pattern of decreased glucose metabolism beginning in certain regions and later spreading as the disease progresses. The extent of this hypometabolism correlates with the severity of cognitive impairment.

A clinical evaluation that incorporates the use of FDG–PET is more accurate than clinical examination alone for the differential diagnosis and identification of various dementia causes. The improved diagnostic accuracy of PET early in the course of a dementia illness leads to more effective disease management. These conclusions are supported by studies showing greater diagnostic accuracy of FDG–PET using neuropathological confirmation of dementia type as the criterion standard of diagnostic accuracy and high predictive value of PET in studies including longitudinal clinical follow-up. Furthermore, the approval by the United States Food and Drug Administration (FDA) of several drugs proven efficacious for the treatment of early, mild Alzheimer's disease brings new urgency to the need for reliable differential diagnostic methods in patients with early symptoms of dementia.

It is also the case that at the stage of mild dementia symptoms in the elderly, about 50 percent of these patients do not have Alzheimer's disease. The addition of PET to the clinical work up provides the most accurate means to separate those who have early Alzheimer's from those who do not. Both outcomes are important for the patient and their family to know.

Finally, the safety of FDG is well established through studies by the FDA, under New Drug Application (NDA) #20–306, and the peer-reviewed literature, representing approximately 2 decades of clinical use of the radiopharmaceutical. No significant adverse reactions attributable to FDG were identified by the FDA or in the general scientific literature involving the use of FDG, nor in a recent article reporting the results of a 5-year prospective study on radiotracers used in nuclear medicine at 18 collaborating institutions. Further, under the approved NDA, FDG has been shown to be safe and effective in brain imaging in patients with epilepsy, another condition in which hypometabolism may exist in specific areas of the brain associated with elliptogenic tissue in the absence of seizures, and there are no new factors introduced in this request to alter the safety profile of FDG.

Importance of Early Diagnosis

The need for early and accurate diagnosis has become more urgent, now that several prescription medications for the treatment of mild to moderate AD are available, as patients with neurodegenerative disease have the most to gain from effective therapies that intervene as early as possible in the course of inexorably progressive irreversible damage to brain tissue. Controlled clinical trials have demonstrated that cholinesterase inhibitors can improve, or delay decline in, memory and other cognitive functions in AD patients. These treatments can cut by more than half the

proportion of patients requiring nursing home placement over a given period of time.

Those studies that have examined long-term effects of cholinesterase inhibitors indicate that drug treatment produces an average delay in cognitive decline in AD patients of 9 to 12 months, relative to the time-course of untreated patients, and a delay in the need for institutionalization of 18 months, which may represent a substantial portion of the patients' remaining life expectancy. Moreover, delaying the institution of therapy by as little as 6 months—in addition to carrying the inherent adverse consequence of depriving the patient of the short-term advantages of potentially enhanced mental activity and diminished cognitive decline during that time—may have long-term disadvantages as well.

Early detection and differentiation of AD offers several additional benefits. For example, many people wish to know about a poor prognosis while their memory losses are relatively mild, in order to better plan for their future. This knowledge allows physicians, patients and family members the opportunity to address safety issues, as well as to identify surrogate decision-makers and sources of caregiver support, early in the disease process when patients can participate in these decisions. Furthermore, such benefits have been shown to reduce the need for nursing home placement of patients with mild dementia by 82 percent, to delay nursing home placement of all AD patients by an average of 11 months, and to generally enhance quality of life for patients and their families. Finally, early accurate diagnostic approaches may also help to avoid the costs, efforts, and frustrations associated with years of multiple diagnostic evaluations. As summarized by the U.S. Agency for Health Care Policy and Research, "early recognition of the condition has important benefits," and yet, "early-stage dementia is often unrecognized or misdiagnosed."

Accuracy of Conventional Work-up for Dementia in Patients With Early Symptoms of Cognitive Decline

How accurate is the conventional diagnostic work-up in the context of evaluating early dementia? This is a difficult question to answer, for at least two reasons. First, clinical definitions of when dementia begins are necessarily arbitrary, as a long period of gradual neuropathologic changes in the brain typically precedes the appearance of cognitive symptoms by years before there are significant enough to clearly fall below the normal range, making disease onset quite insidious. Biochemical changes occur over many years and are more severe than one would perceive from assessments of cognitive decline due to compensatory responses in the brain that act to maintain normal cerebral function in the face of progressive degeneration.

Second, remarkably few studies specifically addressed the question of clinical detection of very mild disease, particularly with comparison to the criterion standard of histopathologic diagnosis. In one investigation aimed at doing so, patients who initially appeared normal or minimally affected were followed with repeated examinations for an average of 4 years. Even by the end of this longitudinal follow-up period of many repetitious examinations, a neurologist examiner detected AD in only 70 percent of the patients who were histologically positive.

In the recent report of the Quality Standards Subcommittee of the American Academy of Neurology, the source of the most comprehensive guidelines and standards for the clinical evaluation of dementia in the last several years, three "Class I" studies were identified in which the diagnostic value of clinical assessment could be meaningfully measured. Class I indicates "a well designed prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, and enabling the assessment of appropriate tests of diagnostic accuracy." Only one of them focused upon evaluating dementia at a relatively early stage. To be included in that investigation, patients were required to have had onset of dementia symptoms within 1 year of entry. All of the 134 patients evaluated underwent a complete standardized diagnostic work-up comprised of a comprehensive medical history and physical, neurological examination, neuropsychologic testing, laboratory tests, and structural neuroimaging, and an average of 3 additional years of clinical follow-up with repeated testing. Sensitivity of this assessment for AD was 83–85 percent, while specificity was 50–55 percent. It should be emphasized that in the studies described above, and in most similar studies, the reported sensitivities and specificities represent not the diagnostic accuracy of initial clinical evaluation, but one that is reached at the end of an entire series of evaluations repeated over a period of years and at a time when AD patients have advanced to more severe stages of disease than when testing was initiated. It should also be emphasized that the accuracy reported with PET is for a single PET scan taken at the stage where the patient has mild disease.

When neuroimaging is obtained in the evaluation of dementia, patients are usually referred for a structural imaging examination—i.e., MRI or CT of the brain.

Conventional MRI or CT of patients with symptoms of dementia may be useful for identifying unsuspected clinically significant lesions (e.g., strokes and tumors), present in approximately 5 percent of patients. However, in patients with AD (which is much more common), such scans are typically read as normal, or as demonstrating the nonspecific finding of cortical atrophy or, worse still, as revealing ischemic changes that are (mis) interpreted as pointing to cerebrovascular disease as the primary or sole process responsible for the patient's cognitive decline—in turn, leading to failure to institute appropriate pharmacotherapy (e.g., donepezil, rivastigmine, galantamine, all of which are FDA-approved only for the indication of "mild to moderate dementia of the Alzheimer's type.").

It is unfortunately not rare for that type of misinterpretation to occur, even among expert clinicians. In a multicenter study involving seven university-affiliated Alzheimer's Disease Diagnostic and Treatment Centers, among patients diagnosed after clinical and structural neuroimaging evaluations as having "vascular dementia," and in whom other dementia diagnoses were specifically thought to be absent, less than 30 percent of those patients actually had isolated cerebrovascular disease, and the majority (55 percent) had AD upon pathological diagnosis. This misdiagnosis can occur because structural imaging positively identified incidental infarcts but AD was transparent to the study.

Accuracy of Dementia Evaluation With use of PET

Investigations into clinical applications of PET with dementia patients stem from numerous studies that have found that many dementing conditions are associated with characteristic alterations in brain detectable with molecular imaging of the biology of disease. PET has been used in research studies of AD and other forms of dementia since the early 1980's, and has been extensively reviewed.

The best studied application of this type is the use of PET with FDG to evaluate AD. Because over 95 percent of the energy (ATP) for the brain to function is derived from metabolism of glucose, PET imaging of glucose metabolism with FDG provides an excellent way to evaluate diseases that disrupt the brain's capability to function normally. By the time patients meet clinical diagnostic criteria for AD, widespread cerebral metabolic dysfunction is usually already present. FDG–PET can thus reveal pathophysiologic alterations associated with AD that occur at the earliest stages of clinical dementia. In fact, the characteristic alterations in glucose metabolism associated with AD can be identified with FDG–PET even before those alterations lead to cognitive symptoms. PET studies published in the *New England Journal of Medicine and Journal of the American Medical Association* by different university scientists have identified metabolic abnormalities of AD at least 5 years before symptoms occur.

Incorporating molecular imaging with PET into the clinical work-up for diagnostic evaluation of dementia could therefore be of considerable help in assisting physicians in meeting the challenge of diagnosing AD earlier and with greater accuracy. Positron emission tomography is of assistance to the clinician in differential diagnosis. Distinguishing among the dementias is critical in making decisions regarding treatment and management appropriate for Alzheimer's, as well as distinguishing which patients who have Alzheimer's from those who don't.

With respect to incremental value of PET beyond clinical differential diagnosis, it was recently shown that among patients having clinical working diagnoses presuming nonprogressive etiologies for their cognitive complaints, those with PET patterns indicative of progressive dementia were more than 18 times likelier to experience progressive decline than those with nonprogressive PET patterns, indicating that the high sensitivity of PET could be used to identify the presence of a progressive dementia among those for whom suspicion of a progressive dementing illness was otherwise low, and thereby lead to earlier institution of appropriate therapy to delay decline.

Conclusion

A higher rate of earlier and more accurate diagnoses of AD and related dementias could be achieved through incorporating PET into clinical management, leading to the most appropriate management for more patients, which in turn would be associated with substantial overall benefit for those patients. It is critically important for standard clinical practice to follow the recent advancements in clinical research identified by the subcommittee, and for health care payors like Medicare to assure that patients and their caregivers have access to these best available diagnostic and evaluative tools. We look forward to working closely with the subcommittee and the Congress on improving both the outcomes and the quality of care received by patients with AD and related dementias.

[Whereupon, at 11:47 a.m., the subcommittee was adjourned.]

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