

ALZHEIMER'S DISEASE, 2002

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ALZHEIMER'S DISEASE, 2002

TUESDAY, APRIL 30, 2002

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN
SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:09 a.m., in room SD-106, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.
Present: Senators Harkin and Specter.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. The hearing of the Senate Labor, Health and Human Services, and Education Appropriations Subcommittee will come to order. I welcome everyone here this morning. I thank you for the tremendous turnout.

This is the third year in a row that this subcommittee has held a hearing on Alzheimer's disease specifically, either with me as chairman or my friend Arlen Specter. I think that is as clear a sign as any that there are no party lines when it comes to preventing and curing Alzheimer's. This is an equal opportunity disease, striking men and women of all races and all backgrounds, so it is fitting that Democrats and Republicans have worked arm in arm to confront it.

The fact that we have held so many hearings on Alzheimer's also shows how urgently we need answers. A poll released this morning shows that 57 percent of Americans are personally worried about getting this disease, and for good reason. There are currently 4 million people in the United States with Alzheimer's and by the year 2050 that number is expected to rise to about 14 million. We will be paying \$357 billion a year in health care costs. That is, unless science can find a way to prevent or delay this disease.

Fortunately, thanks in large part to this subcommittee's effort to double funding at NIH, led by Senator Specter and me, that goal is in sight. Researchers are finally closing in on what causes Alzheimer's. They are using cutting-edge brain imaging to figure out how to diagnose it, and they are studying everything from folic acid and statins to Advil and ginkgo biloba to see if any of these drugs and supplements can help delay it.

On another front, this Nation has finally recognized the importance of family caregivers in helping people with Alzheimer's. This disease takes an enormous toll on caregivers, not only financially but also emotionally and physically. This subcommittee funds two programs to address this need, the Family Caregiver Support Pro-

gram and the Alzheimer's Matching Grant Program, and we will continue to give them high priority.

We are fortunate to have an outstanding panel of witnesses here today to discuss these issues. I of course extend a special welcome to Carol and Gene Gratz of New Hampton, Iowa. It takes a lot of time and courage to come to Washington and prepare for a hearing like this, and I want to thank you and Kris for being here and for helping remind us what it means to battle Alzheimer's and what is involved in caring for a loved one who has been stricken with this disease.

This same goes for the hundreds of patients, family members, and friends in the audience, who are here as part of the Alzheimer's Association's Capitol Hill Day. Your personal stories are worth more than a hundred statistics to Senators and Congressmen that you visit today. I commend you for your advocacy. We need you here and we need you talking to all of your Congressmen and Senators here in Washington.

So before we turn to our witnesses, I would yield to my colleague, the ranking member, Senator Specter, for his opening remarks.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Thank you very much, Mr. Chairman, and thank you for your leadership on the effort to cure Alzheimer's and on matters of medical treatment in general.

Thank you, ladies and gentlemen, for coming here today. This kind of an outpouring of support in one of the Senate's biggest hearing rooms is noted in this city and this country and really around the world.

I thank the Pennsylvania Alzheimer's Association for the Humanitarian Award which I received in this room at the outset of the session. It was interesting to pose for a moment or two for a so-called photo op. I did not realize there were so many cameras in the audience. It is just too bad we cannot take enough time to have everyone photographed individually with Senator Harkin—

Senator HARKIN. So goes life.

Senator SPECTER [continuing]. And I might sneak into the corner of a picture or two. But we have very, very important work to do.

Senator Harkin has noted that he and I and this subcommittee, have led the fight on increasing funding for the National Institutes of Health and Alzheimer's. When we started our effort to double the NIH funding, we asked the Budget Committee for \$1 billion, were turned down, took it to the floor, and lost 63 to 37. So Tom and I got out our sharp pencils and found \$1 billion among the priorities.

Having lost on our effort to increase the funding by \$1 billion, and then the next year we asked for \$2 billion. That is the way things are done in Washington. We got turned down again, and once again we found the money as a matter of priorities.

On this last vote it was 96 to 4 in favor of increasing NIH funding. Through the leadership of this subcommittee, the funding has almost doubled from \$12 billion to \$23 billion. This year President Bush has taken the lead in asking for \$3.4 billion more. So you can see we are on the move.

Last year Alzheimer's was funded at almost \$600 million, and this year we are looking for \$650 million. I know that you ladies and gentlemen are looking for \$1 billion and, frankly, so are we.

I regret that I cannot be present at the news conference later. Today happens to be an exceptionally busy day. They are all busy days around here, but today is an exceptionally busy day because we are going to introduce legislation that will allow nuclear transplantation. Some people call it therapeutic cloning, but that is a misnomer because it gives the impression that it is cloning. Everybody is against reproductive cloning. You certainly would not want to create another Arlen Specter. But if you wanted to create another Tom Harkin, then there would be an argument, an argument in favor.

But very, very seriously, since stem cells came upon the scene in November 1998 this subcommittee has held a series of hearings, 14 in number, to encourage their use because they can be inserted into the brain, and perhaps will be the ultimate answer to Alzheimer's. Now with this nuclear transplantation there is a procedure so that a person suffering from Alzheimer's, Parkinson's, or other maladies, will not reject the cells.

We have got a tough fight on our hands because there are people who want to criminalize cell transplantation. Later this morning we are going to be having a news conference and I am going to have to excuse myself at about 10 o'clock to attend that conference. However, Senator Harkin and I are blessed with fellow Senators here, Senator Taylor, Senator Ellen, and I will be following very closely what we are doing here and fighting very hard to move toward that billion dollars for Alzheimer's and more funding for NIH.

Thank you all for being here and for your battle. Thank you, Mr. Chairman. Thank you, Senator Specter.

STATEMENT OF RICHARD J. HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator HARKIN. Our first witness this morning will be Dr. Richard Hodes. Dr. Hodes, if you could take the witness table, please. Dr. Hodes is the Director of the National Institute on Aging, the lead Institute at NIH on Alzheimer's disease. Dr. Hodes received his bachelor's degree from Yale University, his M.D. from Harvard. He held numerous posts in the National Cancer Institute before being named Director of the National Institute on Aging in 1993.

Dr. Hodes has testified several times before this subcommittee. We certainly welcome him back. So Dr. Hodes, we have your written testimony. It will be made a part of the record in its entirety. If you could sum it up for us, I would certainly appreciate it.

Dr. HODES. Thank you, Mr. Chairman, Senator Specter. It is a privilege to be back before this committee once more, joining the Alzheimer's Association and all present here. I will take these few minutes to summarize for you the progress in Alzheimer's research over the past year. The chairman has adequately summarized the magnitude of the problem and the urgency that faces us and the Nation with an increased number of older people at risk for Alzheimer's disease.

The very positive news is that progress over the past years has been extraordinary. I use the one figure that is in the written testi-

mony as well to illustrate the nature of the process by which basic discovery is translated into application for clinical interventions. Over the past year research on risk factors for Alzheimer's disease has made important progress. Some of the progress was again enumerated in the introduction and has identified factors such as high cholesterol, blood pressure, high homocysteine levels, factors which we are used to thinking of as risk factors for cardiovascular disease and which also appear to be risk factors for Alzheimer's.

The importance of this identification is that it provides targets for modifiable risk factors, and then in fact these are translated into clinical prevention trials currently underway.

Similarly, the discovery of Alzheimer's genes has provided great clues into the mechanisms underlying that process. We have now identified three genes which are responsible for the early onset familial forms of Alzheimer's, as well as one gene, APOE4, that appears to be a risk factor for the common variety of that disease. In the past year it has become evident that an additional four genes are likely to be involved in Alzheimer's and their identification and characterization will again provide new targets for intervention.

Imaging has allowed us for the first time to identify changes in the brain at most early stages, and this is an advance that is critical if we are going to learn how to intervene before irreparable damage has been done to the brain and to follow the effect of therapies by looking at changes in brain structure and function through these imaging techniques.

The past years have provided for the first time animal experimental models of Alzheimer's, which again have proved extraordinarily useful in identifying the mechanisms that mediate the disease and providing ways to test therapies in animal models before their introduction to humans, once identified as being promising and safe. This currently leads to the translation of the information about secretases, for example, the proteins which are important in generating the plaques that characterize Alzheimer's disease, and drugs to inhibit the formation of these amyloid peptides, as well as what you have heard about before, the use of some immunologic approaches to try to clear or prevent the formation of the lesions that characterize Alzheimer's disease.

These all pass through stages of drug development, preclinical testing, and into clinical trials. Whereas a few years ago there were no trials that were targeted at intervening to prevent rather than treat disease, we are now supporting 18 major clinical trials, 7 of which are preventions.

Overall, these past years have seen extraordinary progress. As recently as 15 years ago, we knew essentially nothing about the genetics or underlying molecular basis for Alzheimer's disease. Now we have an extensive knowledge that has been translated into useful information.

As recently as 10 years ago, we knew very little about the early risk factors and our ability to identify early stages of Alzheimer's through imaging was really in its infancy. Over the past 5 years only have we been able to translate this into prevention studies. In the past year alone, we have learned through animal models to recreate ever more valid and legitimate experimental systems which mimic both the anatomic lesions and the memory deficit of

Alzheimer's disease, and these again have provided new and increasing opportunities for intervention.

PREPARED STATEMENT

We have a promise beyond what we expected a few years ago and as we continue in this promise to prevent and treat Alzheimer's disease we continue as well to recognize the need to care for those with Alzheimer's and those many caregivers who are also affected, and so research on trying to ease the burden to caregivers as well as the present quality of life of those afflicted is a part of our research agenda as well.

Again, I thank you for the opportunity once more to appear before you and look forward to answering questions that you might have. Thank you.

[The statement follows:]

PREPARED STATEMENT OF DR. RICHARD J. HODES

Senator Harkin and Members of the Committee: 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 this morning to tell you about the progress we are making toward understanding, treating, and preventing AD.

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

Until very recently, preventing or curing AD was considered, at best, a distant possibility. Our understanding of AD's underlying biology was limited, and for this reason it was difficult even to predict what might be effective as a treatment or preventive.

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

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

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

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

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

In addition to these exciting clinical findings, NIA-supported investigators are beginning to unravel AD's complex etiology. For example, until very recently, just four of the approximately 30,000 genes in the human genome were conclusively known to affect the development of AD pathology. Three of these genes cause early onset AD, and only one is associated with the more common form of the disease, late-onset AD (LOAD). Recent genetic studies suggest that as many as four additional and as yet unidentified genes may also be risk factors for LOAD, and regions in several different chromosomes have been identified as likely locations for these genes. Finding new risk factor genes will help identify pathways affecting the development or progression of AD and may eventually lead to better predictors of the disease even before it is diagnosed.

To facilitate the identification of the remaining AD risk factor genes, NIA is planning an expansion of its National Cell Repository. A national resource for research on AD, the Repository was created to collect and distribute DNA, cells, and information from families with multiple members with AD and related dementias. Its activities include the production of a catalog of cell lines and DNA samples that are available for qualified scientists to study. The expansion will allow researchers to more rapidly identify the underlying genetic mechanisms and environmental risk factors that interact to cause the more common late-onset form of AD. Understanding these mechanisms will provide opportunities for the design of effective diagnostic, therapeutic, and preventive interventions.

The process of translating basic science findings into clinical interventions is a challenging but critical component of AD research. For example, a promising finding gained through basic research efforts was the ability of an immunization strategy to prevent or reverse formation of amyloid plaques in mouse models of AD. In collaboration with NINDS, NIA has issued a Request for Applications (RFA) and funded a number of studies to better understand the science underlying the vaccine approach. Similarly, NIA-funded studies are providing exciting new evidence on the identity of the snipping enzyme that cuts the amyloid beta molecule out of its precursor protein, and ways to blunt its activity. These interventions may be capable of preventing the formation of amyloid plaques.

In addition, NIA-supported researchers have recently made a surprising discovery about the role of amyloid plaques in AD pathology. In one study, investigators found

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

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

³Wilson RS, Mendes de Leon CF, Barnes LL et al., "Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer Disease," *JAMA* 287: 742-748.

that amyloid beta oligomers, or small precursor components of amyloid plaques, inhibited brain mechanisms thought to be involved in memory formation in rats.⁴ In another, scientists used an immunization strategy to treat plaque-containing AD transgenic mice. Although the amount of plaques in the mice's brains remained constant, the mice very quickly regained cognitive functioning.⁵ These findings suggest that amyloid plaques themselves may not be responsible for AD's cognitive symptoms, and that a related pathology—perhaps a precursor molecule such as the amyloid beta oligomer—is the true culprit. This insight, in turn, may lead to the development of new and effective treatments for the disease.

Although the findings are still preliminary, these studies illustrate the importance of continued basic research to help us understand the mechanisms behind AD development and pathology, and the ways in which basic research findings can suggest new prevention and treatment strategies.

Scientists funded by NIA, NINDS, and NIMH are also developing and refining powerful imaging techniques that hold promise of earlier and more accurate diagnosis of AD, as well as improved identification of people who are at risk of developing the disease and a more complete understanding of normal and abnormal age-related changes in the brain. For example, recent studies suggest that positron emission tomography (PET) scanning of metabolic changes in the brain and magnetic resonance imaging (MRI) scanning of structural brain changes may be useful tools for predicting future decline associated with AD and other neurodegenerative diseases.

Researchers have also developed a new way of using functional MRI (fMRI), a technique for visualizing activity of brain structures, that is both easier on the person being tested and capable of imaging smaller structures in the brain than has been possible in the past. Using this new technique, investigators assessed the hippocampus, an area of the brain involved in memory formation, in people between 20 and 88 years of age. They found that activity in certain regions of the hippocampus declines normally with age, but that decline in a specific region, the entorhinal cortex, is abnormal and may reflect an illness or condition such as AD. They conclude that some age-related memory loss is normal, due to ordinary hippocampal changes, but that individuals with dysfunction in the entorhinal cortex may be at increased risk of progressing to full-blown AD.⁶ These studies, if confirmed by ongoing longitudinal observation of the patients, hold the promise, for the first time, of being able to distinguish between the subtle brain changes that occur with normal aging and those that are a harbinger of clinical AD.

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

Another very important area of research involves easing the burden on caregivers of AD patients. In a sense, the AD "patient" is not only the person with the disease, but the entire family unit. Most Americans with AD are cared for outside the institutional setting by an adult child or in-law, a spouse, another relative, or a friend. The financial costs of this care can be devastating to families; the average lifetime cost per person for patients with AD is approximately \$174,000.⁷ In addition to these financial burdens, caregivers frequently experience emotional stress and physical strain.

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

NIA is also supporting a study of a combined behavioral and drug intervention on patients with mild AD. In this study, caregivers will be key participants in the behavioral intervention, and the researchers hypothesize that this participation will reduce caregivers' psychological stress. In addition, NIA is supporting a large, multi-site clinical trial, REACH (Resources for Enhancing Alzheimer's Caregiver Health), to examine the effectiveness of various interventions to strengthen family members'

⁴Walsh DM et al. Naturally secreted oligomers of amyloid β protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* 416: 535–539, 2002.

⁵Dodart J-C et al. Immunization reverses memory deficits without reducing brain A β burden in Alzheimer's disease model. *Nature Neuroscience* 2002: Advance online publication.

⁶Small SA et al. Imaging hippocampal function across the human life span: Is memory decline normal or not? *Annals of Neurology* 51: 290–295, 2002.

⁷Ernst, RL and Hay, JW The US economic and social costs of Alzheimer's disease revisited. *American Journal of Public Health* 84: 1262–1264, 1994.

capacity to care for individuals with AD. Thus far, the study has recruited over 1,200 caregiver/care recipient pairs at six different sites across the country to participate in 12 different interventions. REACH is designed to show us what works to support caregivers and at what cost; we anticipate that the first findings from this trial may be available within the next several years. The NIMH is supporting a major project called the Clinical Anti-psychotic Trial of Intervention Effectiveness for Alzheimer's Disease (CATIE-AD) designed to help identify effective treatments for behavioral problems in AD, to help reduce the burden of care for both providers and families.

Fifteen years ago, we did not know any of the genes that could cause AD, and we had no idea of the biological pathways that were involved in the development of brain pathology. Now, we know the 3 major genes for early-onset disease and one of the major risk factor genes for late-onset disease, and we have extensive knowledge of pathways leading to the development of AD's characteristic amyloid plaques in the brain. Ten years ago, we could not model the disease in animals. Today, transgenic mice are an invaluable resource for modeling amyloid plaque development in the brain and in testing possible therapies. Five years ago, we did not have any prevention trials funded and had no ways of identifying persons at high risk for the disease. Now, we have seven ongoing prevention trials, and scientists are identifying persons at high risk for developing AD by imaging, neuropsychological tests, and structured clinician interviews. And as recently as one year ago, we did not understand anything about how plaques and tangles relate to each other. Now, through the creation of the first double transgenic mouse to produce both plaques and tangles, we know that plaques in the brain can influence the development of tangles in brain regions susceptible in AD. Recent findings also suggest that there are some common mechanisms of disease in a number of neurodegenerative disorders, which will further inform research in AD.

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

Thank you 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.

Senator HARKIN. Dr. Hodes, thank you very much.

I am going to ask you to stay, if you could, and we will have the next panel up.

I will yield to Senator Specter. He does have to leave.

Senator SPECTER. Thank you, Mr. Chairman. I appreciate the opportunity to ask a few questions of you, Dr. Hodes, at this time because I am going to have to excuse myself, as I said earlier.

The funding for Alzheimer's, as well as the funding for all of the other National Institutes of Health, depends to a significant extent on the sense of the Congress, really the sense of the American people, as to how well the money is being spent and what are the results. We have had estimates on Parkinson's, for example, that we may be within 5 years of a cure.

While I know it is difficult to make a quantitative evaluation, I would be interested, to the extent that is consistent with your scientific methodology, if you can give us some estimate as to a time line for a cure on Alzheimer's?

Dr. HODES. Well, I apologize for the fact that I think I cannot responsibly quote a specific time in terms of years. But I can certainly share an exceptional sense of optimism projecting from the pace of discovery as summarized over these past 15 years. This pace is bringing us closer to interventions and cures than we ever dreamed possible a few years ago.

The fact that we were able to bring into clinical trials interventions which have the promise for preventing disease is extraordinary. I can tell you that the results of some of these ongoing prevention trials, for example, will be coming to fruition over the next

3 to 5 years. That is not an estimate of when we know we will have success, but it is an estimate of when we should have the first results on some of the large-scale prevention trials which have real promise of success.

Senator SPECTER. So you are saying, in terms of prevention, the prospects are good that the scientific research has a realistic possibility of preventing Alzheimer's?

Dr. HODES. Yes. I think that we have over these past years uncovered now multiple potential targets. We have identified risk factors and learned how to modify those risk factors. Some of these risk factors are behavioral, some of them are biochemical and genetic. The more targets we have for intervention, the greater the chance that one or more of them is going to be successful. And yes, the pace of progress over these past years gives good reason to propose a realistic vision of a cure and/or prevention for Alzheimer's disease over the years to come.

Senator SPECTER. When we talk about raising the funding this year by approximately \$50 million, from \$600 to \$650 million, what tangible evidence can you give Senator Harkin and myself as ammunition to deal with our colleagues in the Senate as to why that increase ought to be given? What can you tell us that we can pass on to the other Members of the Senate?

Dr. HODES. I can provide some general statements and then some rather more specific. In the general sense, the greatest argument for a continued increase in funding is the quality of scientific opportunities. Each discovery, be it in genetics, in risk factors, in relief of caregivers, creates opportunities, which then need to be followed by additional research.

In particular, as basic research has provided opportunities for treatment and prevention, we have come to a stage of carrying out multiple clinical trials. Now, if we were to carry out only one clinical trial at a time, awaiting its result before going on to the next, I think this would be an unpardonable delay in eventually reaching success. So our approach has been to capitalize on the funding that has been made available to fund all of the most outstanding opportunities for clinical trials.

Clinical trials, for prevention in particular, require the inclusion of thousands of individuals followed for several years. They are expensive studies. Each of these studies may cost in the range of \$25 to \$50 million. In order to carry out those several, each of which is responsive to outstanding current scientific opportunities, an increase in budget would be enormously helpful and important.

Senator SPECTER. Okay. The billion dollar question. Dr. Hodes, what can you accomplish with \$1 billion that you cannot accomplish with \$650 million?

Dr. HODES. Well, we would be able, simply arithmetically, by that comparison to support 50 percent more research than we do. Fifty percent more research would easily be carried out by supporting uncompromised quality of both basic science to try to produce the opportunities for translation in the years to come as well as an increased speed of expeditiously following up on current opportunities to follow all of the candidate interventions for both treatment and prevention.

Senator SPECTER. Dr. Hodes, I would like you to give some thought when you go back to your office, to your laboratory, to see if you can quantify more specifically. I appreciate the answers you have given, but we started funding Alzheimer's with \$3.9 million in 1976 and now it is up to \$600 million and you want to go to \$1 billion. To the extent that you could give some hard estimates or some hard information—for example my colleagues can understand that you could possibly get 50 percent more research from \$1 billion versus \$650 million. That kind of arithmetic is about the limit of our capability.

But see if you cannot give us something really tangible, as tangible as possible.

Dr. HODES. Absolutely. I would be pleased to provide concrete examples.

[The information follows:]

Recent research advances have created important new opportunities for research that will accelerate progress toward interventions for early diagnosis, treatment, and prevention of AD.

Recent scientific advances, largely the result of NIH-supported research, have illuminated significant genetic and cellular mechanisms that underlie AD. For example, four genes that affect the development of AD have already been identified, and recent studies suggest that for late-onset AD (the more common form of the disease) there may be at least four more risk factor genes. Efforts to pinpoint their exact location will help identify pathways affecting the development or progression of AD and may eventually lead to better predictors of the disease even before it is clinically apparent.

In addition, scientists are developing and refining powerful imaging techniques that target anatomical, molecular, and functional processes in the brain. These new techniques hold promise of earlier and more accurate diagnosis of AD, as well as improved identification of people who are at risk of developing the disease. For example, recent studies suggest that positron emission tomography (PET) scanning of metabolic changes in the brain and magnetic resonance imaging (MRI) scanning of structural brain changes may be useful tools for predicting future decline associated with AD and other neurodegenerative diseases. Researchers have also developed a new method of functional MRI (fMRI), a technique for visualizing activity of brain structures, that is both easier on the person being tested and capable of imaging smaller structures in the brain than has been possible in the past. These methodologies may also be useful for evaluating the efficacy of drugs in stemming the progression of AD or preventing its onset altogether. However, these and other emerging imaging techniques, while promising, require further testing and analysis before they can be routinely adopted in the clinical setting.

Research findings at the molecular level have created new and unprecedented opportunities for translation of basic research into clinical applications. The process is necessarily deliberate; as new target molecules are identified, interventions must be developed, tested in animal models for safety and efficacy, and only then moved into human trials. At the same time, clinical trials are needed today to test treatment interventions that have already shown promise in animal models, including promising new vaccines that “wash” amyloid from the brain and treatments that target enzymes called secretases, which begin the formation of amyloid plaques in the brain by snipping a protein into fragments that re-form as plaques. This research area is of tremendous interest to researchers in industry and academia as well as at other NIH Institutes, and this interest is leading to expanded opportunities for partnership.

Trials are also needed for interventions that prevent AD onset or progression. Examination of a number of possible AD preventives is underway—for example, the AD Prevention Trial using vitamin E and donepezil, as well as trials testing the effect of estrogen, anti-inflammatory drugs, and antioxidants. Candidate interventions that lower amyloid burden in animal models of AD are being identified with increasing frequency. Targeting specific abnormal cellular pathways uncovered by recent discoveries, including plaque and tangle formation and death of brain cells, are pointing to design of new interventions to prevent the onset of AD. Prevention trials are among the most costly of research projects, but, if successful, the payoff in terms of reduced disease and disability will be significant.

Critical opportunities that could be supported with increased funds in fiscal year 2003 include:

(1) Epidemiology studies to identify additional genetic causes and risk factors for AD, information that will provide new targets for treatment and prevention.

(2) Testing of new methods for early diagnosis of AD, based on imaging and markers of early brain changes. Early diagnosis is critical to effective treatment and prevention, before onset of symptoms and death of brain cells.

(3) Pre-clinical trials in newly created animal models of AD, which permit rapid testing of potential treatments based on new genetic and molecular targets.

(4) Clinical trials of AD prevention. Candidates for prevention, based on human epidemiology and animal model studies, require clinical trials. These include anti-inflammatory agents, anti-oxidants, estrogen, statins, immunization with amyloid peptide, and secretase inhibitors.

(5) Development of interventions to reduce caregiver burden and strengthen family members' capacity to care for AD patients.

It must be noted that this estimate is based on our assessment of scientific opportunities over the next five years, without consideration of economic constraints or other competing priorities of the Federal government. This level of support must be integrated with other research efforts of the NIH.

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

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Specter.

I just noticed, looking at the record, we have got it pretty even. When I was chairman we almost doubled it and when you were chairman we almost doubled it. That is pretty good.

Senator SPECTER. It looks like if we have another change in chairmanships we will double it again.

Let me tell you ladies and gentlemen, while I prefer to be chairman to ranking, when Senator Harkin and I shift the gavel it is seamless, absolutely seamless. It keeps going the same way.

Senator HARKIN. That is true, absolutely.

Thank you very much, Dr. Hodes.

I would like to call up our next panel if I could then. Orien Reid, Chair of the National Board of Directors; Dr. Marilyn Albert; Carol and Gene Gratz; and David Hyde Pierce. We will go in that order, and I would first recognize Ms. Orien Reid, the Chair of the National Board of Directors of the Alzheimer's Association.

Ms. Reid was a consumer reporter on television and radio for 26 years and recently formed a media consulting business. Ms. Reid earned her bachelor of arts degree from Park College and a master's degree from the Atlanta University School of Social Work. She lives in Laverock, Pennsylvania. I am not sure I know where that is, but it sounds like a nice place to be.

Ms. REID. Suburban Philadelphia.

Senator SPECTER. One additional comment about Ms. Reid, Mr. Chairman. She is a very, very familiar figure on Philadelphia television and when she speaks people listen.

Senator HARKIN. Politicians listen, right?

Senator SPECTER. So do statesmen.

STATEMENT OF ORIEN REID, CHAIR, BOARD OF DIRECTORS, ALZHEIMER'S ASSOCIATION

Ms. REID. Thank you. Thank you, Senators. Thank you, thank you so much.

Senator SPECTER. Adlai Stevenson defined a statesman as a dead politician.

Ms. REID. Well, I am not ready to die.

Thank you so much. Thank you, Senator Specter.

Senator HARKIN. Orien Reid, welcome. All your statements will be made part of the record in their entirety. If you would just sum it up for us, I would appreciate it. Again, I thank you for your great leadership.

Ms. REID. I certainly will. Thank you so much for inviting me to testify at this very important hearing today. As you noted, I serve as Chair of the National Board of Directors of the Alzheimer's Association.

I am here this morning to speak for my own family because, you see, today is a very special day. It is my mother's birthday, and had she not been killed by Alzheimer's disease she would be 86 years old today. So I just feel her spirit with me today and I want to speak for her and for my grandmother, my aunt, and my uncle, all of whom had Alzheimer's disease.

I also speak for the hundreds of families, Alzheimer's families who are gathered in this room today, and for the millions of families like us. We are here today to thank you for your consistent leadership on issues that matter to the Alzheimer's community. We are here to tell you that we support your continued efforts to increase funding for Alzheimer's research and services. We know that you are on our side. We are here to enlist others to support your effort to increase medical research funding in general and specifically for Alzheimer's disease.

Now, I would like to submit and present to you for the record the Alzheimer's national public policy program to conquer Alzheimer's disease. You will have that. Today Alzheimer's advocates from across the country will deliver this national program personally to their own Senators and Representatives.

My request today is an urgent one. It is to ask you to increase appropriations for Alzheimer's research by \$200 million this year and to a billion dollars a year as soon as possible.

We thank you for your support of our goal, which in particular we are very happy that you chose to reflect it as part of the language of your committee report last year. We have seen your commitment to Alzheimer's disease research funding through the years.

The problem is we are running out of time to find an end to this disease. It is time now. The time is now for Congress to make this investment. The two experts in Alzheimer's research that I have sitting here will tell you about, and Dr. Hodes has just told you about, some of the scientific opportunities that exist today. If we are going to prevent the 14 million baby boomers from getting Alzheimer's disease, we have got to do something today.

The experts know the science, but I along with 19 million other caregivers know what it is like to live with this disease. I watched Alzheimer's disease destroy my mother, a beautiful woman with a beautiful mind, a woman who counseled eminent leaders like Dr. Martin Luther King Junior and the former Mayor of Atlanta, Maynard Jackson.

My family and I made major sacrifices and I do not regret that a bit. But what I do regret is the fact that this disease robbed my children of their childhood. It also took the money that I had saved for their college education and it left scars that continue to affect their lives. Today my children and I all live in fear because we do

not want to live this nightmare all over again. I am only 16 years younger than my mother was when she was diagnosed with this disease. It is also very disconcerting to me to learn that African Americans may be at a higher risk for Alzheimer's disease. That does not make me feel comfortable.

Today there are 14 million baby boomers in the United States who will get Alzheimer's disease if we do not find a way to stop it. We cannot save Medicare if 14 million baby boomers get Alzheimer's disease because the cost of treating people with Alzheimer's disease is estimated to climb from \$31.9 billion in 2000 up to \$49.3 billion in 2010, just 8 years away, even though Medicare does not pay for most of the long-term care.

We cannot preserve Medicare and Medicaid if we do not find a way to stop this disease. That can only be done through research.

In addition to research, there are some important programs before your committee. We are happy to hear that you are going to continue your support of the family caregiver support program and we urge you to continue your support to expand the Alzheimer's matching grant program to all 50 States, to reach rural, underserved, and minority populations.

PREPARED STATEMENT

You can see how your support has helped thousands of their families with Alzheimer's disease. As my beloved friend Maureen Reagan used to say, she hoped that we would be the last generation to face this disease without hope. You are our only hope so that we will not have to. Please help us.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF ORIEN REID

Senator Harkin, Senator Specter and other members of the Subcommittee: Thank you very much for inviting me to testify today at this very important hearing. I serve as chair of the Board of Directors of the Alzheimer's Association. I am here to speak for my own family—my mother, my aunt, my uncle, and my grandmother—all of whom had Alzheimer's disease. I also speak for the hundreds of Alzheimer families gathered in this room today, and for the millions of families like us across the country.

We are here to thank you for your constant leadership on issues that matter to the Alzheimer community, and to tell you that we support you in your continued efforts to increase funding for Alzheimer research and services. We know you are on our side. We are here to enlist others to support your effort to increase medical research funding in general, and specifically for Alzheimer's disease.

I would like to present to you and submit for the record the Association's National Public Policy Program to Conquer Alzheimer's Disease. Today, Alzheimer advocates from across the country will deliver this National Program personally to their own Senators and Representatives.

Today I am here with an urgent request—to ask you to increase appropriations for Alzheimer research by \$200 million this year, and to \$1 billion a year as soon as possible. We applaud you for your support of our goal, reflected in the language of your Committee Report from last year and your commitment to Alzheimer's disease research funding through the years.

There is no time to wait—now is the time for Congress to make this investment. You have two experts in Alzheimer research here to tell you about the exciting scientific opportunities that exist today—new opportunities we must pursue in order to prevent 14 million baby boomers from getting Alzheimer's disease. I will leave the discussion of the science to the researchers—my knowledge is in the area of what it means to live with Alzheimer's disease.

My own personal experience with this horrible disease reflects those of 19 million Americans who have a family member with Alzheimer's disease. Our experiences,

combined with the knowledge that the Alzheimer's disease process begins in the brain as many as 20 years before a person is seriously impaired, have created our sense of urgency and driven us to this call for action.

It devastated me to watch the disease destroy the beauty and mind of my mother—a woman who had counseled imminent leaders like the late Dr. Martin Luther King, and former Atlanta Mayor, Maynard Jackson. My mother's Alzheimer's disease forced major changes in my personal and professional life. I don't regret those sacrifices for a moment. My mother was worth it. But this disease didn't just take a toll on me, but also robbed my son and daughter of their childhood, took the money I had saved for their college education, and left an indelible mark on them that continues to affect their lives.

My children and I are terrified by the prevalence of this disease in our family. I'm now 16 years younger than my mother when she was diagnosed with Alzheimer's. My greatest fear is that it has started to eat away at my brain too, and that my children will be forced to live this nightmare all over again. Recent studies showing that African-Americans may be at higher risk of Alzheimer's disease does nothing to ease my mind.

I am not alone in my fears. Today there are 14 million baby boomers in the United States who will get Alzheimer's disease, if we don't find a way to stop it. Think about the implications. For example, it is difficult to see how you can save Medicare, if 14 million baby boomers get Alzheimer's disease. Alzheimer's poses a threat to Medicare even before the baby boomers have all retired. The cost to Medicare of treating people with Alzheimer's disease is estimated to soar from \$31.9 billion in 2000 to \$49.3 billion in 2010, even though Medicare does not pay for most of the long term care they need.

The survey conducted by Peter D. Hart Research Associates and being released today by the Alzheimer's Association found that Americans are also concerned about health care costs. More than eight in ten voters say that paying for health care costs is the biggest financial challenge facing the elderly today—far outpacing housing, the cost of utilities and food. There is no way to preserve Medicare and Medicaid, and rein in health care costs, if we do not find a way to stop Alzheimer's disease, and that can only be done through research.

In addition to medical research, there are important programs before your Committee that are providing immediate help to people who are living with Alzheimer's disease. We urge you to continue your long-standing support, and fund further expansion of the Alzheimer matching grant program to support model programs in all fifty states to reach underserved communities, particularly minority populations and rural areas. And we thank you for your support of the Family Caregiver Support Program.

The Alzheimer's Disease Demonstration Grants to States Program helps states assure that community services are accessible and appropriate for the unique needs of people with Alzheimer's and their families. While these grants are very small—\$250,000 to \$350,000 per year for a three-year period—they have had a huge impact by:

- providing services to individuals who were previously left out, especially minorities and rural populations;
- changing the larger health and long term care systems so that states do a better job of serving people with Alzheimer's disease;
- developing partnerships along with new public and private resources to continue and expand programs upon conclusion of the demonstration;
- developing “best practice” service delivery models that are being replicated within and beyond the state; and
- generating an Alzheimer's Disease Resource Room on the Administration on Aging website that features information on successful strategies that can be replicated in communities across the country.

Let me give you a few examples of the innovations your investment has brought in the states that have received these grants:

- In Maine, dementia teams that are linked to university specialists now go to the homes of people in isolated rural areas and regularly consult with their family physicians.
- A mobile dementia day care program now serves small towns in Georgia that cannot support a full time adult day care center.
- Latino families in South Central Los Angeles now have a comprehensive Alzheimer community services program, and the initial seed money from the federal government has been totally replaced with locally raised funds. This program has now been replicated in the African American and Asian American communities.

—Oregon has trained all of the case managers in its long term care system to understand the special needs of people with dementia and, as a result, the entire system is more responsive to those needs.

—A current grant in Rhode Island is focused on developing a model of consumer directed respite care provided by and for minority elders. It is also creating a model of workforce development, including Certified Nursing Assistant (CNA) training and the establishment of career ladders for CNA's.

In each case, the state has partnered with local Alzheimer's Association chapters to apply for and implement the grant. We urge you to appropriate \$25 million to allow these innovations to go forward in every state. As states and health care systems redefine their services to meet the needs of a growing aging population, this program will help assure that people with Alzheimer's disease do not fall through the cracks.

Alzheimer's disease is an epidemic, and we simply cannot wait to do something about it. The Alzheimer's Association continues its own investment in Alzheimer research—nearly \$120 million to date. We will do everything we can to bring as much private money as we can into the search for the answers. But we all know it will take your support, and the resources of the NIH to harness and stop this disease.

To allow researchers to capitalize on new knowledge gained through past investments in research and reach answers in time to make a difference, Congress must provide an additional \$200 million this year for a government-wide assault on Alzheimer's disease. We are asking you to join us in this effort. Time is running out for our children and grandchildren, and for 14 million baby boomers who may be living with a sentence of Alzheimer's disease. Please, for all of us, act now. Thank you.

Senator HARKIN. Thank you, Ms. Reid. Great testimony. Thank you for your leadership.

Next we will turn to Dr. Marilyn Albert, Professor in Psychiatry and Neurology at Harvard Medical School and Director of Gerontology Research Unit at the Massachusetts General Hospital. Dr. Albert also serves as Chair of the Alzheimer's Association's Medical and Scientific Advisory Committee. She received her Ph.D. in psychology from McGill University. Welcome, Dr. Albert.

STATEMENT OF MARILYN ALBERT, Ph.D., CHAIR, MEDICAL AND SCIENTIFIC ADVISORY COMMITTEE, ALZHEIMER'S ASSOCIATION

Dr. ALBERT. Thank you very much, Senator Harkin, Senator Specter. It is a great honor to speak to you this morning in my position as Chair of the Medical and Scientific Advisory Committee of the Alzheimer's Association.

I wanted to begin by commending you for your past and very strong support of research funding for the NIH and for Alzheimer's Association in particular. My research colleagues around the country are certain that it is that strong support that has enabled us to learn so much about Alzheimer's disease so quickly over the last 20 years. We believe it is this progress that has put us on the brink of finding truly effective treatments for the disease in the coming years.

In my written statement that I submitted for the record, I identified five major research areas where we believe an infusion of money would be greatly helpful. But in the brief time allotted to me, what I would like to do is talk to you about the research area that I know the best, the one that I work in, which is longitudinal clinical research for the early diagnosis of Alzheimer's disease.

As you may know, recent studies have demonstrated that the pathology of Alzheimer's disease begins many years before clinical dementia can be diagnosed. Most of my colleagues believe that when we get effective treatments for the disease it is highly unlikely that they are going to be benign, and yet it is going to be critically im-

portant to intervene before substantial damage has been done to the brain.

So the kind of work that I do has been involved in trying to identify people before the disease symptoms become full-blown, when intervention would be of the greatest benefit. The work of my research colleagues and of several other groups around the country has been using cognitive testing, neuro-imaging, genetics to try to identify individuals who have memory problems that are relatively mild and be able to predict when those symptoms are going to progress and which of those individuals are going to go on to meet criteria for Alzheimer's disease in subsequent years.

Now, when I started this phase of my work 10 years ago, it seemed sort of incredible in retrospect, but I thought that we would have clear answers within 5 years. It turns out, on the basis of our research, that people progress with varying rates, people with mild memory difficulty. Some progress quite quickly and do develop Alzheimer's disease within a very short period of time. Some progress very slowly and seem to be going in the direction of developing the disease, but do not within even a decade. Some who appear to be at high risk actually remain stable, and we have a great deal of difficulty then predicting what is going to happen to people over time.

So that, although we have made a great deal of progress, it has been much harder than we ever anticipated, it has required much more time, many more subjects, and of course that translates into many more dollars.

We believe that we are on the right track. We have anticipation that pharmaceutical companies will be close to adopting some of the methods that we have used to help screen drugs that might be effective for the disease and study patients to determine whether or not the drugs that they have developed actually slow down the progress of the disease. But it is really going to take considerably more effort to get the answers that we are seeking.

This one research effort I think illustrates how much more complicated and expensive long-term clinical research is on a day to day basis and why it is so important for us to have additional research dollars for this problem as well as the many others that Dr. Hodes just described.

PREPARED STATEMENT

Like my other colleagues in the Alzheimer's Association, I want to emphasize how important it is for us to have additional funding for research in this area. As Orien just said to you, it is not an exaggeration to say that if we do not find effective treatments for Alzheimer's disease there is no health care system in the world that will be able to support the problem that we will face.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF MARILYN ALBERT

Mr. Chairman and members of the Subcommittee: Thank you for inviting me to participate in this very important hearing on Alzheimer's disease—the epidemic of the 21st century. Others on this panel are here to describe the human side of Alzheimer's and its enormous cost—to individuals, to families, to our health care system and our national economy. The case for the war against Alzheimer's is clear.

My task, as a scientist, is to convince you we can win this war—if we are willing to put the resources into the fight.

The possibility of ending Alzheimer's disease as we know it has never been more real. We have reached this historic point because of your unflagging support of funding for the National Institutes of Health as a whole, and for Alzheimer's disease research in particular. We are now poised to yield enormous return on that prior investment.

When I started my own research on Alzheimer's disease 22 years ago, there were a relative handful of scientists working in the field. NIH was investing about \$12 million in Alzheimer research. We were just beginning to understand the basic mechanisms of the disease. Only a handful of papers on Alzheimer's disease found their way to publication. Caregivers struggling with the disease were starting to find each other and forming the local support groups that would soon become the Alzheimer's Association.

How the world has changed! This July, the Alzheimer's Association will convene the 8th International Conference on Alzheimer's Disease and Related Disorders in Stockholm. More than 4,000 scientists working on Alzheimer's disease will gather to report new findings on the biology, epidemiology, genetics, environmental risk factors, diagnosis, treatment, and prevention of Alzheimer's disease. This year alone, more than 3,000 peer-reviewed papers on Alzheimer's research will appear in leading American and international journals.

We have come this far, this fast, because of the systematic care with which the National Institute on Aging has nurtured and developed the field of Alzheimer research, creating a scientific infrastructure that has made possible not only the rapid accumulation of knowledge, but an unprecedented sharing of data among laboratories and the translation of basic science to clinical studies.

All of this work is directed toward two objectives:

First, to delay and prevent the onset of disease in the tens of millions of people who are now at risk. We now understand that the process that leads to Alzheimer's may start in a person's brain many years before he or she becomes clinically impaired. That gives us a window of time to prevent the devastation of Alzheimer's in millions of today's babyboomers—if we can find effective and affordable therapeutic interventions, and if we can identify those individuals who are at risk so that we can intervene early enough to make a difference.

The second and equally important goal is to treat and delay the progress of Alzheimer's in those for whom we cannot prevent disease.

Both of these goals are within reach. But Alzheimer's disease has turned out to be much more complicated than we originally thought. That is why we need a \$1 billion investment from NIH, to pursue simultaneously the immediate opportunities in 5 essential and interrelated areas of research.

First, we must continue basic biomedical research to find the last pieces of the complex puzzle of Alzheimer's disease, to complete our understanding of how and why brain cells shrink and die. We are constantly learning more about the two major characteristics of Alzheimer's—the amyloid plaques and neurofibrillary tangles—and how they interact. We know how plaques are formed and deposited in the brain and how they act as toxins. Now, scientists are working aggressively to block their formation. We are assembling the same type of information about the formation of tangles. And evidence is mounting that inflammation and oxidative stress may play an important role in the disease. Neuroscience, and the study of Alzheimer's disease particularly, is one of the most exciting and promising areas of basic science today. We will continue to attract the best minds to the field as long as we maintain our investment here.

Second, we must conduct large scale clinical trials to test potential therapies to slow or halt onset and progression of disease and to prevent or delay disability. Basic research is identifying multiple targets for such therapies, and observational studies have suggested that drugs already used widely by middle-aged and older people may have a protective effect. The only way to figure out how to turn all of this discovery into safe and effective treatment is to do large-scale, controlled clinical trials of each of these interventions that holds promise.

These trials—especially prevention trials—are very expensive. We have to recruit large numbers of people who do not yet have Alzheimer's disease and follow them long enough to see whether the compound has the desired effect. And we have to test for variability by race and ethnicity. At the urging of Congress and under the leadership of the National Institute on Aging, NIH is investing in a number of these trials already, at costs as high as \$25 million for a single trial. But if we are going to take advantage of the window of time we have before large numbers of babyboomers succumb to the disease, there must be a steady infusion of funds for

additional trials to validate initial results and to explore new potential therapies as rapidly as science identifies their potential.

Third, we have to do the longitudinal clinical studies that will tell us who is really at risk of getting Alzheimer's disease and to find the surrogate markers that will make it possible to identify people before the disease is apparent. We are not just doing science for science's sake. We have a moral obligation to make sure that the people who can benefit from what we learn get the treatment they need, and that they get it early enough to make a difference.

This is the kind of work I do. For the past 10 years, my research team has been following people with mild memory difficulty to try to see if we can predict which ones will get worse and which one's won't and what factors influence progression. We started with a relatively small group of subjects, but as we learned more about how complicated the disease is and how slowly it progresses, and as other research has brought us new tools and new questions, our research has grown. We have increased the number of people we are following. We are looking at people who are normal as well as those with memory difficulties. And we are now able to take the enormous scientific progress that has been made by others and apply it in our clinical studies. When we started, we were excited that we could use CAT scans to "see" the brain. Now, we are using three types of structural imaging that give us extraordinary ability to measure changes in the brain over time. We are applying increased knowledge of genetics to look at its influence on cognitive performance and imaging measures in our subjects. We have also been able to confirm the findings of other researchers by looking at the impact of anti-inflammatories in our population.

All of this takes money. Our own research—this one clinical study, for example—now costs \$2.5 million a year. And it requires a sustained commitment of funds for a decade or more. Without a continued substantial increase in funding from Congress, NIA will be forced to make impossible choices between multi-year funding for these large scale clinical studies and funding for new investigator-initiated basic science. If we are going to find the answers to Alzheimer's in time to make a difference, there must be enough money in the system to do both.

Fourth, we need to track down the linkages between vascular disease and Alzheimer's. This is an increasingly promising avenue of research with enormous potential payoff. Evidence from a number of longitudinal studies here and abroad suggests there is a direct relationship between vascular disease and Alzheimer's. Vascular abnormalities in the brain, on top of the lesions of Alzheimer's disease, appear to make cognitive impairment worse. Vascular risk factors like high cholesterol and high blood pressure may be significant risk factors for Alzheimer's disease as well. And there is now some accumulating evidence that statins—cholesterol-lowering drugs—may have a protective effect.

Many of the long-term population-based studies of heart disease, like the Framingham Study and the Nurses Health Study, now have cohorts that have aged. These studies have accumulated a lifetime of data on their subjects, which we can examine now to study the risks for cognitive decline.

The public health implications of this avenue of research are enormous, particularly for racial and ethnic groups disproportionately affected by vascular disease. We already know a lot about primary and secondary prevention of vascular disease. Now, we may have a route to prevention of Alzheimer's as well, for a significant number of people at risk. It will take increased resources at the National Heart, Blood, and Lung Institute as well as the NIA to pursue this research as rapidly as possible.

Fifth, we must find more effective ways to treat Alzheimer's disease. No matter how quick and successful we are in finding a way to prevent Alzheimer's disease, millions of Americans like Mr. and Mrs. Gratz will still be living with a diagnosis of Alzheimer's for the foreseeable future. Congress must continue to invest resources in the search for more effective and affordable treatments to improve the quality of life and delay the disabling impact of the disease. This requires investment in:

- drug discovery for direct treatment of Alzheimer's and for the management and treatment of the behavioral symptoms that make care so difficult and costly;
- health services research and demonstrations to find effective ways to manage comorbid medical conditions in people with Alzheimer's who cannot self-manage those conditions and to prevent avoidable illness, injury, and hospitalization;
- social and behavioral research to improve the quality of care and the quality of life for persons with Alzheimer's and their caregivers in every setting.

The Alzheimer demonstration grant program, which other witnesses have discussed, is a critical piece of this research agenda. I join in urging the subcommittee to increase funding of that highly successful program to \$25 million to allow all 50 states to participate.

In conclusion, I want to acknowledge the enormous task this subcommittee faces in balancing the competing demands in this most important part of the federal budget, which touches so directly on the health and well-being of every American family. Finding room in that budget for the investment needed to keep 14 million Americans from getting Alzheimer's disease is one of the most important things this subcommittee can do for our long term economic and social security. Thank you.

Senator HARKIN. Thank you very much, Dr. Albert.

Next we turn to Carol and Gene Gratz, who are from New Hampton, Iowa, a small town that I have been to many, many times in the northeastern part of the State. Gene was diagnosed with Alzheimer's last June. Carol and Gene have been married for 12 years. They are here with their 11-year-old son, Kris.

Again, I want to thank you both for taking all the time and the trouble to travel here and to give us some personal insight as to what has happened to you just in the last year or so since Gene was diagnosed. So Carol, we will recognize you if you would like to kick it off.

STATEMENT OF CAROL GRATZ, NEW HAMPTON, IA, EAST CENTRAL IOWA CHAPTER, ALZHEIMER'S ASSOCIATION

Ms. GRATZ. Mr. Chairman and members of the subcommittee: Thank you very much for giving me the opportunity to testify this morning. I am truly honored to be here representing my home State of Iowa and our East Central Iowa Chapter of the Alzheimer's Association. My name is Carol Gratz and I am here today with my husband Gene and our 11-year-old son, Kristopher, who is sitting right behind me.

We have traveled here to Washington from New Hampton, Iowa, a rural community of approximately 3800 people, to ask you to please do everything to increase funding for the Alzheimer's research so a cure or prevention can be found as soon as possible. Our plea for increased research funding is extremely personal. Ten months ago Gene, at age 57, was diagnosed with Alzheimer's disease.

The symptoms of Gene's disease actually started appearing 4 years ago. Gene at 53 began having problems with his short-term memory and was having great difficulty in dialing a phone or reading a newspaper. Naturally, our first instinct was to see an eye doctor. However, the eye doctor could find no medical explanation for Gene's vision problems.

Over 2 years, he continued to have problems with his vision and his memory, but rarely complained, so I was not fully aware of the extent of Gene's problems. By this time he was having trouble driving and also decided he could no longer endure a 2-hour daily commute to his job as a forklift driver. He found a new job as a produce manager closer to our home and he worked there for about a year. The produce manager's job involved substantial amounts of paperwork, which he had great difficulty doing because of his vision problems.

In January 2000, Gene changed jobs a second time and wound up with a position on an assembly line at a local manufacturing plant. The assembly line work involved repetitive tasks and did not require reading or writing, so Gene did well at his job.

However, in April 2001, with a slowdown in the assembly line, it forced him to switch jobs in the plant, and he had to begin to

read blueprints, which he had trouble doing as his vision was very poor. His supervisor asked him to visit a doctor for a checkup.

By this time I knew that Gene's vision problems and short-term memory problems were not normal and began researching his symptoms on the Internet. My search took me to the Alzheimer's Association web site. I contacted our local chapter and the people at the East Central Iowa Chapter were extremely helpful, and sent us many information packets as well as a list of doctors in our community.

After seeing a general practitioner and multiple visits to various specialists, we were referred to the University of Iowa hospital for additional testing. Finally, in June of 2001 we got the terrible news that Gene had Alzheimer's disease. We were also told that he had a rare form of the disease that attacked his eyesight as well as his memory.

As you might imagine, in the past year it has been very difficult for our family in many ways. Gene can no longer work, drive a car, or read a newspaper. He has also had to give up his favorite hobby of woodworking because his doctor has told him it is not safe to use power tools.

Gene is on one of the newer Alzheimer's medicines, which helps maintain his moods and his functions. His doctor evaluates him every 6 months, but we are putting a lot of miles on our car as we must travel 2½ hours to Iowa City for every appointment. There are no doctors in our local community specializing in Alzheimer's.

I have had to switch jobs, dealing with unsympathetic employers who would not grant my repeated requests for time off to take Gene to multiple appointments in Iowa City. I was lucky enough to find a job closer to home at a manufacturing plant. My employer is very accommodating and sympathetic and I currently work the third shift from 8:30 p.m. to 6:30 a.m., which allows me to be home with Gene during the day and help my son with his homework after school and also fix dinner for my guys before going off to work.

While the disease has been very difficult on Gene and me, it has been especially difficult for our son, Kris. He is 11 years old and seeing his father struggle to do many things that other dads do is very tough.

Gene and I learned a great deal about Alzheimer's. I know the scientists are studying the genetic aspects and that is why we have chosen to advocate for increased research funding, in hopes that a cure or a prevention can be found soon to save our son from this dreadful disease.

We also want to let people know that Alzheimer's is not just for seniors, it is for younger people, too.

I would like to thank you very much for giving me the opportunity to be here today and I commend you for everything you have done to help the Alzheimer's research and funding. Thank you very much.

I would like to introduce my husband, Gene, to say a few words.
Senator HARKIN. Thank you, Carol.
Gene.

**STATEMENT OF GENE GRATZ, NEW HAMPTON, IA, EAST CENTRAL
IOWA CHAPTER, ALZHEIMER'S ASSOCIATION**

Mr. GRATZ. Senators Harkin and Specter, I am very, very happy and really feel privileged to be here. My eyesight, like Carol says, is not real good. I had to make kind of a scribbly-scratch notepad. She did a pad for me on a tape recorder, but it is kind of hard to listen to that too and still talk to everybody.

But the worst thing, I guess, in this whole deal: I lost my oldest boy, 18 years old, in a car accident, and now I am going to lose my son, Kris, to Alzheimer's, and I am the one that has got it. He is going to be without a father eventually. Hopefully it is not going to be soon. The doctors tell me it is going to be a long time down the road.

But we need the funding. We need that extra funding to get this thing killed and get it dead. That is the only reason I came here.

The paperwork that I was given, I really cannot remember most of it. But I can tell you that I raise a few small animals, about all I can do anymore. I have got a new Dodge pickup sitting in the garage that I cannot drive. And my son wants to drive already, but good old Marty, our sheriff in town, he says I cannot teach him out in the field. But Kris wants to know how.

PREPARED STATEMENT

But anyway, it makes life miserable. I was extremely independent all my life. I ran major businesses. And to have it happen to me like this—it came from my father and my grandfather. We have got to stop it in this generation, have got to stop it. I do not care what it costs. We have got to get the funding in some way, shape, or form to get this disease killed.

Thank you very much, gentlemen. I wish I could be of more assistance, but I did my best I could do. Thank you.

[The combined statement follows:]

PREPARED STATEMENT OF CAROL AND GENE GRATZ

Mr. Chairman and members of the Subcommittee: Thank you very much for giving me the opportunity to testify this morning. I am truly honored to be here, representing my home state of Iowa and the East Central Iowa Chapter of the Alzheimer's Association.

My name is Carol Gratz and I am here today with my husband, Gene and our 11-year old son Kris, who is sitting right behind me. We have traveled to Washington from New Hampton, Iowa, a rural community of approximately 3,800 people, to ask you to please do everything you can to increase funding for Alzheimer research so that a cure or prevention can be found as soon as possible. Our plea for increased research funding is extremely personal because 10 months ago, at the age of 57, Gene was diagnosed with Alzheimer's disease.

The symptoms of Gene's disease actually started appearing about 5 years ago. When Gene was 53, he began having some problems with his short-term memory and his vision. He complained of not being able to see very well and was having great difficulty dialing the telephone and reading the newspaper. Gene went to the eye doctor, who did not find any explanation for the vision problems.

Since the eye doctor could find no explanation for Gene's vision problems we did not pursue the issue. Gene continued to experience difficulties with his vision and memory for another two years but he rarely complained, so I was not fully aware of the extent of his problems. He was also having trouble driving and decided that he could no longer endure the daily two-hour commute to his job as a forklift operator at a John Deere warehouse. He found a new job as a produce manager at a small grocery store much closer to our home, and we thought that would solve all of his problems. Gene lasted about a year at his new job but the amount of paper-

work he was required to do combined with the frequent inventory reports caused him a lot of stress due to his continuing vision problems.

In January 2000, Gene left the small grocery store and took a job on the assembly line at a plant that manufactures horse trailers and trailers for NASCAR races. Since the assembly line work involved repetitive tasks and did not require reading or writing, Gene was able to handle the job. Gene was doing well until April 2001 when a slowdown in assembly line work forced him to switch jobs in the plant. In his new assignment, Gene was required to read blueprints, which was impossible for him to do with his poor vision. Gene told his supervisor that he was having trouble reading the blueprints and his supervisor suggested that he visit a doctor for a check-up.

By this time, I knew that Gene's vision and short-term memory problems were not normal and with my daughter's help, began researching his symptoms on the Internet. Our search led us to the Alzheimer's Association website and we contacted our local chapter. The people at the East Central Iowa chapter were extremely helpful and sent us an information packet as well as a list of doctors in our community. We went to a general practitioner, a neurologist and a neuropsychologist. We were also referred to the University of Iowa hospitals for additional testing. Finally, in June 2001, we got the terrible news that Gene had Alzheimer's disease. We were also told that Gene had a very rare form of the disease that was attacking his eyesight as well as his memory.

As you might imagine, this past year has been very difficult for our family in many ways. Gene can no longer work, drive a car or read the newspaper. He has also had to give up his favorite hobby of woodworking because his doctor told him that it is not safe to use power tools anymore.

Gene is on one of the newer Alzheimer's drugs which is helping to maintain his functioning and mood swings. His doctors evaluate him every six months but we are putting a lot of miles on our car because we must travel two and a half hours to Iowa City for every appointment. There are no doctors in our rural community who specialize in treating Alzheimer's.

I have had to switch jobs and deal with an unsympathetic employer who would not grant my repeated requests for time off to take Gene to his multiple appointments in Iowa City. I was lucky enough to find another job, closer to home, at an employee-owned manufacturing plant. My new employer has been very accommodating and sympathetic. I currently work the third shift, from 8:30 p.m. until 6:30 a.m., which allows me to be home with Gene during the day, help Kris with his homework after school and fix dinner for "my guys" before going off to work. This schedule also gives me piece of mind since Gene and Kris are generally sleeping during the hours that I am at work and I don't have to worry about their safety.

While this disease has been hard on both Gene and me it has been especially difficult for our son Kris. He is only 11 years old and seeing his father struggle to do many of the things that other dads do is very tough. With assistance from the Alzheimer's Association, we found a counselor who has been working with Kris to help him cope with the changes we've experienced due to Gene's diagnosis.

Gene and I have learned a great deal about Alzheimer's and we know that scientists are actively studying the genetic aspects of the disease. We worry that Kris is at risk and we've chosen to advocate for increased research funding in the hope that a cure or prevention will be found and our son will be spared from this dreaded disease. We have also decided to speak out about Alzheimer's to let everyone know that it is not just older people who suffer from the disease. Younger people get it too and the impact of Alzheimer's is especially painful when it strikes early. Alzheimer's has taken so much from our family. It has robbed Gene of his career and hobbies and has threatened our financial future. But worst of all, it has stolen Gene's second chance at being a father. Gene's son from his first marriage was killed in a tragic car accident a few years before we met so we were thrilled when we learned that I was pregnant with Kris and that Gene would get another chance at fatherhood.

In closing, I want to thank you again Senators Harkin and Specter for giving me the opportunity to share how Alzheimer's disease has impacted my family. I commend you for all that you have done to increase research funding and raise awareness about Alzheimer's and am grateful for your leadership in the U.S. Senate. As you will hear from the others who are speaking today, scientists are on the verge of finding ways to prevent and treat Alzheimer's disease and the actions we take today may save future generations—including my son—from this devastating illness. Thank you.

Senator HARKIN. Thank you both very much.

You said you want to be of more help. What you are doing is of immense help. We must put a human face on this. Senators, Congressmen, researchers have to know the human toll that this is taking. These are not just statistics. They are real people with real families, working hard, getting hit like this.

The fact that you, Carol—just think about that, everybody. She works from 8:30 p.m. to 6:30 a.m. every night so she can be home to get Kris off to school, get him home from school, take care of Gene during the day. That is the kind of toll it takes on families. You are a brave woman, and you are a brave man.

Mr. GRATZ. She is, she is a fantastic woman, and I thank God I married her.

Senator HARKIN. You are lucky to have her for a wife, I will tell you that. She is great.

Mr. GRATZ. I have got a piece of gold sitting next to me and I know that.

Senator HARKIN. So thank you very much for sharing your story with us.

Mr. GRATZ. Thank you very much.

Senator HARKIN. Now we turn to David Hyde Pierce. I did not know that was his real name. I always thought it was Niles Crane. So we all know Niles from Frasier. He has won three Emmy Awards, a Golden Globe Award; obviously, someone that is known nationally.

He is also a national board member of the Alzheimer's Association and an extraordinarily committed advocate in the effort to cure Alzheimer's. Mr. Pierce testified before the subcommittee last year and, Niles, we certainly welcome you back again.

STATEMENT OF DAVID HYDE PIERCE, ACTOR

Mr. PIERCE. Thank you, Dr. Harkin. I appreciate that.

Senator HARKIN. The floor is yours. Thanks.

Mr. PIERCE. I am very pleased to be back here. Thank you for inviting me back to testify.

My grandfather, my father, and, I recently found out, one of my dad's sisters all suffered from Alzheimer's and dementia. In my written testimony I say that over the years my fears of Alzheimer's have increased, but I have to tell you, sitting here today, listening to the breakthroughs in research and the leadership that people like Orien provide and the incredible bravery of Gene and Carol and their son, Kris, my fears have evaporated and they are replaced by hope and determination.

We are so close to catastrophe and we are so close to a cure. That is why I am here urging you, in spite of the enormous challenges you face today, to maintain your commitment to medical research for Alzheimer's and as soon as possible to increase funding to a billion dollars a year.

Today the Alzheimer's Association is releasing a national survey by Peter D. Hart Research Associates regarding Americans' feelings about Alzheimer's disease. The survey confirms what I have seen every day, that Americans of every age are terrified by the threat of Alzheimer's disease and that they overwhelmingly support the shared efforts of this committee and the Alzheimer's Association to increase funding.

I am going to give you just some of the results. Ninety-five percent of Americans believe that Alzheimer's disease is a serious concern for this country. Senators Harkin and Specter, you have led this Congress in the effort to double funding for the NIH. The survey shows that Americans support the work. In fact, in this election year these voters say medical research is one of the most important areas for Federal spending, ranking second only to education and ranking above military spending.

Three-quarters of Americans specifically support the proposal to increase funding to \$1 billion a year. Here is the amazing thing: 77 percent of people 65 and older support that, which you would expect, but 75 percent of Americans 18 to 34 also support this increase in funding.

Mr. Chairman, members of the committee, we understand that the world has changed since we were all here last year, and we understand that because of that there are many competing priorities before this subcommittee. But one of the lessons that we have learned over the last months is that when Americans are faced with a real threat and a terrible enemy, we stand together and we marshal our resources to fight.

For 14 million Americans, Alzheimer's disease is that threat. Alzheimer's disease is that enemy. The case for increasing funding to a billion dollars is overwhelming and the support for increasing funding is overwhelming.

PREPARED STATEMENT

You by convening this hearing demonstrate your own concerns about this looming crisis and your dedication to preventing it. I want to thank you on behalf of the Alzheimer's Association, on behalf of all the families dealing with this disease, on behalf of everyone in this room, and certainly today in honor of our dear friend Maureen Reagan, for whom this was her greatest goal.

Thank you very much.
[The statement follows:]

PREPARED STATEMENT OF DAVID HYDE PIERCE

Mr. Chairman and Members of the Subcommittee, thank you for inviting me back to testify before your Subcommittee. As you know, I am a National Board member of the Alzheimer's Association. You have heard my personal story before. Both my grandfather and my father died of Alzheimer's disease.

With each year that passes, my fear grows—my fear that the disease process that destroyed their memories, and ultimately their lives, has begun developing in my own brain. My fear grows not just for myself, but also for my generation—the 14 million baby boomers who will get Alzheimer's disease if we don't find a way to beat this dreadful disease.

At the same time, my hope grows. Today I testify with more enthusiasm, more confidence that scientists are on the verge of a breakthrough. My hope is joined with a sense of urgency. In the quest to find a breakthrough for Alzheimer's disease, this nation is in a race against time.

In the midst of the enormous challenges you face, I urge you to maintain your commitment to medical research funding for Alzheimer's disease, and increase funding to \$1 billion a year as soon as possible. In this race against time, we can't afford to slip.

Today, the Alzheimer's Association is releasing a national survey by Peter D. Hart Research Associates regarding Americans' concerns about Alzheimer's disease. I ask that the survey analysis be submitted for the record. This survey confirms what I see every day—that Americans of every age are terrified by the threat of Alzheimer's disease, and that they overwhelmingly support the shared efforts of this

Subcommittee and the Alzheimer's Association to increase funding for Alzheimer research to \$1 billion annually. I would like to share just a few of the findings from the survey.

Ninety-five percent of Americans believe that Alzheimer's disease is a serious problem facing our nation. Perhaps they know as well as we in this room do—our window of time is very short. Perhaps they know that this disease can strike anyone, even a President of the United States.

Senator Harkin and Senator Specter, you have led this Congress in the effort to double funding for NIH. Our survey shows that Americans support your work. In fact, in this election year, voters say medical research is one of the most important areas for federal spending, ranking second only to education spending, and placing ahead of spending on the military.

More importantly, however, to those of us who sit before you today—three fourths of Americans agree with the proposal that Congress should increase funding for Alzheimer research to \$1 billion per year. There is a broad coalition of voters who unite behind this proposal, with large majorities of both young (75 percent of 18–34 year olds) and old (77 percent 65 years old and older) agreeing that funding for Alzheimer research should be increased.

Half of us in the room already have the time bomb of Alzheimer's disease ticking away in our brains, each and every day. Congress must find a way to defuse this bomb, before it destroys our brains and ultimately our entire selves.

The American people have every right to be afraid of this horrible disease. By the middle of the century, 14 million of today's baby boomers will have Alzheimer's disease. For most of them, the process that will destroy their memories, their lives, and their savings has already begun.

Mr. Chairman. We know there are many competing priorities before this Subcommittee, and we understand the fiscal constraints you face as you balance those priorities. But as we look to the future of the 14 million baby boomers and indeed, the future of each and every American, the case for \$1 billion investment in Alzheimer research is overwhelming. This hearing demonstrates your own concern about the looming crisis and your commitment to averting it. On behalf of everyone in the Alzheimer's Association, for every family dealing with Alzheimer's disease, and for all of us sitting here before you, thank you.

Senator HARKIN. Thank you very much.

Dr. Hodes, do you want to come back up. We have got an extra chair there. Just join David there.

I again know he has to leave soon, but I would yield to Senator Specter for any comments or questions.

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

I want to thank especially Mr. and Mrs. Gratz for coming in and providing some real insights for not only this subcommittee, but really for all America, on the kinds of difficulties which you have had to face. You are very brave and I thank you for coming in.

I would like to ask Ms. Reid and Mr. Pierce, with the family backgrounds that you have and with the obvious additional risks which you face, Orien, what do you think about the intensive work being done by NIH to try to prevent the onset of Alzheimer's?

Ms. REID. I think NIH has been doing an outstanding job and I am looking forward. You know, we can invest at the Association, we already have invested almost \$120 million into research. But we know that the real resources come from NIH. They are the ones who are going to be able to really jump-start the effort and continue at the pace that they are continuing at to find a cure for this disease.

I am absolutely desperate for us to find a way to prevent this disease.

Senator SPECTER. Mr. Pierce, how do you look to your future?

Mr. PIERCE. Well, I tell you, what I have noticed, I have worked for the Association for a few years and I have used this quote of 14 million in the year 2050 so often I have forgotten that that 14

million is not going to happen in the year 2050. It is happening now. I have friends who are beginning to suffer from this. I look to my brother and my sisters and other members of my family and I just wonder when.

So I applaud the NIH for its efforts, but I am really impassioned about doubling our research while there is time.

Senator SPECTER. Dr. Albert, in your capacity as a psychiatrist would you care to offer an opinion as to the desirability of having people at random take a test to find out what their gene consistency is, the so-called genome, with a view to seeing if there is some latent problem that a person may have which could be acted upon in a preventive way? Or does it open up Pandora's box for too many worries that you cannot really effectively deal with?

Dr. ALBERT. As you probably know, there are four genes that have been identified that are associated with risk for Alzheimer's disease, and three of them are fortunately extremely rare. They only affect people who are primarily young and they occur in families where in every generation multiple individuals have the disease. These genes are dominant genes, which means if you carry the mutation you will definitely get the disease.

For those individuals, genetic testing along with genetic counseling is often available. It is not discouraged if people understand the consequence of finding the answer and if the genetic counselors feel as if it is appropriate to do the testing.

The other gene that we know about is a gene that increases risk for Alzheimer's disease late in life. All of us carry some form of that gene and all that it does in its particular risk form is to increase the likelihood that you will get it across your lifetime. That is called the APOE gene and it is the APOE4 form of the gene that increases risk.

There are multiple organizations, health care organizations throughout the country, that have met and determined that this sort of genetic testing is not to be recommended because it does not tell you within a short period of time what is going to happen to you. In fact, in my own research we have looked at that gene and we have tried to see whether or not it tells us, if you have trouble with your memory, whether or not you will get Alzheimer's disease in 4 or 5 years. It is of no informative value. It does not help at all.

But in general, people feel that knowing that you have a slightly increased risk by having genetic testing is not to be recommended.

Senator SPECTER. Thank you very much, Dr. Albert, and thank you all. Senator Harkin has urged me to urge you to get behind us on this nuclear transplant issue. You ladies and gentlemen come from all over the country. Our staff can tell you which Senators need to hear from you. If you are from Tennessee, illustratively, and you write to your Senators, Dr. Frist for example, that could be very, very influential. He is the one physician in the Senate, and he is not alone in needing convincing.

We have a very, very tough battle and your lives, the lives of your loved ones, and the lives of millions of Americans may need to turn on the availability of nuclear transplants. To criminalize that kind of medical research and tie the hands of scientists, will drive many scientists out of the United States to other countries,

will severely impact medical research, and severely impact the ability of medical research to find a cure for Alzheimer's.

Thank you very much, Mr. Chairman.

Senator HARKIN. Thank you, Senator Specter.

I just wanted to echo what Senator Specter just said. There is so much confusion out there on this issue. I do not know of anyone that I have really met, I do not know of anyone on this committee or in the Senate, that is in favor of human cloning. We are all opposed to human cloning. That is not somatic cell nuclear transplantation.

So a number of us have bills in to criminalize, actually criminalize, and put severe civil penalties on anyone who would transplant that to a uterus for the purpose of human life. But to cut off the research for nuclear transplantation and the great promise that it holds to me is just really unconscionable, to try to cut that off when so many people are suffering and this holds such great promise for so many people.

So we are going to have a big debate here in the Senate in May on this issue, probably before the Memorial Day break. But I think it is going to be an extremely, extremely close vote. So we really need your help.

Dr. Hodes, you talked about a study in which scientists used an immunization strategy to reverse the formation of the amyloid plaques in mice. I have followed this quite closely and we really got excited about it because it looked like it might be a possibility for the development of vaccine for Alzheimer's.

But then I was surprised when I picked up the paper and read that the vaccine was permanently shelved after 15 patients who were taking it developed meningitis. Can you inform us or enlighten us a little bit about this? What happened? Are we still looking at a possible vaccine? Just what has happened to that, because it looked like it was so promising.

Dr. HODES. Yes, I can relate to you in a limited extent at least what occurred. I say limited extent because this was a study that was carried out by a pharmaceutical company, Elan. NIH was not involved in its support and so I do not have the level of information that I might otherwise have.

But precisely as you described, on the basis of animal experimentation, humans were immunized with an amyloid peptide that was designed to treat the buildup of that protein abnormally in the brains of individuals with Alzheimer's disease. In the first phase of the study, a number of individuals were treated with one immunization to see if any side effects would appear. In that initial study there were none.

The study then moved on to a second stage, in which individuals were immunized multiple times, which was the process that appeared to be effective in the mouse and animal models. It was a number of individuals after the second immunization who developed symptoms consistent with inflammation of the brain and spinal cord and led to the cessation of the study.

In answer to your question about what this means for the future, I think it is important to understand that, although this is enormously disappointing, that it is not entirely unexpected nor un-

usual that the first attempt at a new approach to treatment is met with the discovery of side effects.

The National Institutes of Health continues to support basic research looking at alternative strategies that use immune therapy targeted towards finding something that will be therapeutic without the unacceptable side effects that occur. So the very impressive initial scientific discoveries remain reason for hope. There is continued experimentation to try to find nontoxic variants of an immunization approach to Alzheimer's disease, all this at the same time that we examine the alternatives, other approaches, as many as we can find in opportunities provided by basic research at multiple levels.

Senator HARKIN. So there is under your Institute some ongoing basic research into immunological approaches, for example?

Dr. HODES. Yes, precisely so. In an initiative that was encouraged by the White House 2 years ago and was funded last year, there is specifically funding of a large cohort of investigators who are looking at different aspects of immune approaches to Alzheimer's disease in animal model systems.

Senator HARKIN. These initial studies by Elan—they went through all the safety tests, so it was pretty shocking that it turned out like that. Again, you are right, this was not an NIH thing. This was through a private drug company.

But can you assure me that there are researchers that are being funded by NIH that are looking at what happened and perhaps sort of, in my own nonscientific way of saying it, backing down from that and starting over again with that type of research on a vaccine?

Dr. HODES. Certainly attempts to try to—

Senator HARKIN. Let me say this. We are trying to find out, why did it not cause the inflammation in mice? It passed the safety studies, then, as you mentioned, after multiple vaccinations resulted in problems. Well, there is something in there that needs to be looked at. I was just wondering, is NIH funding any research in the area to find out what might have gone wrong there?

Dr. HODES. The NIH is funding research looking at approaches in animal models to determine which of them might be more or less prone to the kind of complication that you mention. Actual studies on the patients who underwent these clinical trials and who suffered the side effects is being carried out by Elan and those precise studies on those patients are not a part of NIH-supported research.

But certainly the efforts to understand what in immune therapy is likely to cause those side effects and how it can be avoided is most certainly a part of the ongoing research supported by NIH.

Dr. ALBERT. Senator Harkin, if I might just add one brief word. As Dr. Hodes mentioned, we do not know all the details of what went on because it was done by the pharmaceutical company. But the initial safety studies were done with a very small number of people. I think it was no more than about 30 people that were in those studies. In the larger trial there were over 300, and that is when you increase the possibility of having side effects. So I think that is the primary reason why the side effects were not identified early on; and as Dr. Hodes said, because they gave multiple injec-

tions and it was only after two or more that people developed side effects.

But there are many reasons to be optimistic, because the particular strategy that they used included a large portion of this protein that we know to be important for Alzheimer's disease. Some people feel, for example, that if they used a smaller part of the protein it might be just as efficacious and not harmful.

Senator HARKIN. So you think it still holds some promise?

Dr. ALBERT. Absolutely.

Senator HARKIN. And we should continue the research and development into that.

Dr. ALBERT, one other aspect of this that is intriguing to me is this idea of use it or lose it, using your brain. Someone told me you are working on a book about that right now.

Dr. ALBERT. That is correct. It is very nice of you to ask.

Senator HARKIN. Well, let us talk about this book.

Dr. ALBERT. It is called "Keep Your Brain Young."

Senator HARKIN. When can we expect it out?

Dr. ALBERT. It is actually out right now.

Senator HARKIN. Oh, it is?

Dr. ALBERT. Yes, within the last few weeks.

Senator HARKIN. Oh my goodness. Well, I will have to get a copy of that. What are you advocating?

Dr. ALBERT. In fact, research has shown over the last decade or so that it is important to be both physically and mentally active. It makes sense to us that being mentally active might be helpful to the brain, form more connections, but recent research has demonstrated that physical activity seems to work and interact with mental activity to be beneficial for the brain.

Basic animal research suggests that that might be because the brain releases certain kinds of protective factors that help it respond to injury. There is very recent exciting research that being physically active in a so-called enriched environment helps with neurogenesis, the generation of new nerve cells, particularly in the part of the brain that has to do with memory.

So there are several avenues that people can take just in their daily lives to maximize function.

Senator HARKIN. In your book are you specific to saying do certain things? Are there certain types of things?

Dr. ALBERT. The book is based on scientific evidence and so we outline a number of things that are available. As Dr. Hodes mentioned, there are a number of prevention trials that are ongoing looking at the effects of vitamin E, ibuprofen, statins, estrogen. We talk about those as well. We talk about the importance of stress and data on the fact that high levels of stress hormones in the brain are bad for it.

Senator HARKIN. Let me ask another question to anyone here. Again, there is a lot of talk, I do not know if studies have been done, or at least preliminary types of things, to indicate that certain types of vitamins, folic acid, maybe some of the B vitamins, ginkgo biloba, others—in fact, before my older brother passed away a couple of years ago he had been having some problems with memory, and his doctor actually prescribed ginkgo biloba to him to

take, which I found interesting. This would be 3, almost 4 years ago now.

What can you tell us about that? Antioxidants, things like that, these are things I read about, but is there any basis for that at all, Dr. Hodes?

Dr. HODES. I think for each of the agents you have mentioned—and we can discuss them in more detail—the answer is yes, there is something to it. Yes, there is a basis for considering the possibility they will be effective, but for none of them is there as yet definitive incontrovertible evidence of effectiveness.

Those are precisely the situations where we think it important to conduct rigorous clinical trials as expeditiously as possible. So that currently for vitamin E, for other antioxidants, for folate, for B12, for ginkgo biloba, among other agents, there are prevention trials that are currently in progress. These are randomized trials in which the individuals taking the drugs or supplements, the physicians who are taking care of them, do not know the identity of the drug.

Then over a period of years observations will determine whether those individuals who did or did not take a particular agent are more or less likely to develop Alzheimer's disease. These studies most definitely have the ability to determine whether there is a significant effect of these agents or not. We have every reason to hope that one or more of them will be effective. But at the same time we convey this optimism, it is important to convey to the public that none of them is yet proven and none of them can be recommended in the absence of further scientific evidence.

Senator HARKIN. Any other observations on that at all?

Ms. REID. No, except to tell you that I take them all.

Senator HARKIN. Well, I would guess on that side they cannot harm you.

Dr. HODES. I guess responsibly it is important to qualify that last statement, that they cannot harm you. Certainly if these agents were absolutely without risk it would be hard to deny the logic that says why not try them. But in fact, even for the most benign of them, agents such as vitamin E, it has been shown that at some of the dosage levels that people are taking that they can interact with other drugs and can predispose to problems. So that one does have to be quite cautious.

Senator HARKIN. Well, you are right in terms of interaction with other drugs and stuff. That is why we always say you should make sure that your health care provider knows all you are taking and stuff like that, and do the research and do your own reading on it yourself, and take matters into your own hands.

But I am not certain, Dr. Hodes, that I would agree fully with you on that. Certainly anything taken in excess can hurt you. An aspirin, if you take a bottle, will kill you. People die every year. We have hundreds of deaths in this country from aspirin. But to take things like, I do not take ginkgo, but vitamin E or folic acid, the B drugs, I think taken in dosages that have been at least recommended by various studies over the years, I cannot see how that would ever harm anybody.

Obviously, if you overdosed or something like that on anything—

Dr. HODES. I think I agree very much with what you said. It is important to distinguish between recommendations that are well-founded on experience or doses of vitamins, including folate or the B vitamins—quite right, there are recommendations for daily intake that are consistent with health and have minimal side effects.

But for some of the agents being recommended, being used by some for treatment or prevention of Alzheimer's, the evidence is simply not clearcut, and it is in those cases where the risk of overdosing, if you will, exists, because what constitutes a safe or dangerous dose is not as well determined as it is for some of these other agents.

Senator HARKIN. One of the reasons I have been pushing for years for that National Center on Complementary and Alternative Medicine to do more research in that area, because the RDA's that we have today were established—help me out here—60 years ago, something like that?

Dr. HODES. Many are quite old, correct.

Senator HARKIN. I think they are 60 or 70, something like that. The recommended daily allowances were set up as the minimums, as I understand it, to prevent things like vitamin C deficiencies. They were set up as the bare minimums that you need.

Other medical researchers over the years have said, well, that may be fine, but in some of these cases actually boosting those levels up will help your immunological system.

So I am not certain that just taking RDA's or recommended daily allowances is effective at all in some of these cases. I know I will bet you there are millions of people out there leading healthful lives that take much more than the recommended daily allowances of a lot of different vitamins, like E and A and everything else. But again, we need more research in that area.

Dr. HODES. That is certainly an area I think where we agree entirely on that last statement. We in studies such as the ginkgo biloba trial are working closely with Steve Strauss and the National Center for Complementary and Alternative Medicine to assure that the best kind of science is applied with an open mind to the efficacy and safety of agents such as this.

Senator HARKIN. I might just say, for the benefit of everyone here, that there is really pretty extensive research going on through that National Center on ginkgo biloba. I assume you work together with them on that, Dr. Hodes. Do you?

Dr. HODES. We do. That study is being carried out collaboratively with that center.

Senator HARKIN. Very good.

Mr. Pierce, you may have told us last year, but remind us: How old were your father and grandfather when they were diagnosed?

Mr. PIERCE. We noticed the symptoms in my grandfather in his mid-eighties. Well, actually in his case the diagnosis was done on autopsy after he passed away, which was in his early nineties. My dad was in his late seventies, early eighties. I actually do not know about his sister, but they were of a contemporary age, so I imagine it was the same.

Senator HARKIN. Is it not true you really cannot diagnose still today Alzheimer's until you do an autopsy? Is that not right, Dr. Hodes?

Dr. HODES. That is true, that is the definitive test. But the ability to diagnose during life has improved greatly with more extensive testing of biology function imaging, so that in the hands of people well versed the accuracy of that diagnosis can be in the range of 90 percent or more.

Senator HARKIN. Getting to the funding level, you mentioned how many people would be affected in the future and you are right, that baby boom generation is here now. They are alive right now.

We have all this talk about what we are going to do to save the Medicare system because of the onset of the baby boom generation and people living longer. A lot of people are scratching their heads on how to fund it.

I saw a figure about a year ago that said that if we could just delay the onset of Alzheimer's by 5 years, we would have no problem in Medicare funding. That would decrease the cost of Medicare so much that we would have no problems. Think what it would do if we could actually find a cure of Alzheimer's. Then we really could provide prescription drugs for everyone under Medicare and things like that.

Eighteen clinical trials, is that what you said, Dr. Hodes?

Dr. HODES. Correct.

Senator HARKIN. Can you give us some idea of some that you think really are looking good?

Dr. HODES. We do not have information from them as they are in progress. The way that these studies are done, because they are masked or blinded so that individuals do not know what they are taking, leads to the consequence that in general we do not know the outcome until a study is over. Now, it is monitored carefully and confidentially, so that if we should find an overwhelming positive result or evidence of toxicity, a negative effect, early, the study would be stopped. But this is the unusual circumstance. So in general we will not know the outcome until the studies are terminated and the data analyzed.

Senator HARKIN. I am just going to ask a question of everyone in the audience. How many people here in this audience today take multi-vitamins on a daily basis and supplement that with maybe other doses of vitamin E or the B vitamins or vitamin C or other things like that? I am just curious as to how many people do that here. How many people here take that on a daily basis?

[A show of hands.]

Look around, Dr. Hodes. I'd better raise my hand, too, because I do also.

I think there is a great sense among people that somehow we know what our bodies are telling us, that we need this, and we better get the researchers going on this. That is not in your bailiwick. That is in that other center, NCCAM. That is why I am trying to push them.

I will close up. Again, talking about the caregiver portion of this, we cannot lose sight of the fact that as we proceed in the funding for research that we have to be very cognizant of support for caregivers. The toll that this takes on families is incredible. The Gratzes, it just tears our hearts out.

I have been blessed in my own family. We have not really had Alzheimer's in my own family, but we do have very dear and close

friends with this disease. Joann Hutchins, who I have known all my adult life, is now in a nursing home and does not recognize her husband. Watching this as a close personal friend, it is just mind-boggling what this does to families.

My elementary school teacher lived across the street from me until about 5 years ago. Mary King was wonderful. She actually got me started in school. She was the first one who ever read a book to me. All of a sudden, she got hit with Alzheimer's. It came on really suddenly, like within a year, and she could not take care of herself, and now she is in a nursing home. So you see, we just have to make sure we do not forget about that aspect of it, the caregivers.

To the Gratz family, you are extremely courageous. All I can say is, Kris, you chose well when you chose these parents, I can tell you that. They are very brave parents. We need them to keep telling their story. I know it is tough, but people have to understand the human dimensions of this. These are not just statistics on pieces of paper. These are our friends, our relatives, our loved ones, our family members.

I have found around here that many times the most powerful way to get to someone here is just to give them that human story. That is what we need you to do while you are here today and tomorrow, I do not want to say lobbying, I want to say educating the Members of Congress. But do not take no for an answer. Get in to see these people, because obviously we do what we can here, but we need support—I mean we here on this committee—we need the support of our fellow Senators.

I will say right here now to all of my friends who are here, I love you dearly and this is a cause of mine that I took up a long time ago. I might just say again—I should have said this when Senator Specter was here. I said when I was chairman we doubled Alzheimer's funding, when he was chairman he has doubled it. Well, now it is my turn again, and I intend to do it again.

But we need the support of our fellow Senators to do this. I cannot do it by myself and Senator Specter cannot do it by himself. The two of us working together can do a lot, but we cannot do everything. We do need a lot of help here and we need help in the House of Representatives, too. That is why it is so important what you are doing here.

I just cannot tell each of you how important it is for you to get to these offices and to talk to people and bring them the human dimensions of what we are talking about. And yes, tell them about Medicare, tell them about the impact on the money. They need to understand that, too.

We will continue to do our job here to support Dr. Hodes and the National Institute and to support all of NIH here. It is not just in Dr. Hodes' Institute. There is research that affects this in just about every Institute, I think, going throughout the whole spectrum of the Institutes at NIH. Dr. Hodes has the lead agency, but there are a lot of others that are out there.

So again, I just want to thank you all for being here.

Orien, thank you very much for your great leadership. You are a wonderful spokesperson. You get the point across. You have a

great persona. We need people like you to get those points across. So God bless you and thank you so much.

David, thank you again also. People look to people like you. You are a well-known person in this country and people like you. Again, your persona comes across as someone that people like and they trust. Your words, your leadership, can be very powerful in moving us here and getting the American people to understand the dimensions of this. So I congratulate you. I thank you for the leadership.

To Dr. Albert and to Carol and Gene again, please continue to tell your story and please continue to get the word out on what we can do. Hopefully, we are going to have some breakthroughs here. You are a young man and hopefully pretty soon we are going to have some breakthroughs here that will help you out. That is my fervent hope, my wish, and now we have just got to get the money behind it.

Mr. GRATZ. I really appreciate you guys letting us be here. I guess one thing we have to do with Alzheimer's, when times are bad you have got to laugh at it a little bit. It makes the day go better. Sometimes you have got to act a little crazy, but that is okay, too, because it makes your day go better.

The folks in New Hampton, I want to get them out of their houses instead of hibernating anymore. I mean, I walk around, I was kind of pushed aside for quite a while until they finally realized that I was the sort that was not going to go away.

Senator HARKIN. Good for you.

Mr. GRATZ. And I will be there until the Lord says it is time for me to leave.

Senator HARKIN. Just remember, you are not alone. You have got everybody here. You are not alone and we are with you.

CONCLUSION OF HEARING

Thank you all very much for being here, that concludes our hearing.

[Whereupon, at 10:29 a.m., Tuesday, April 30, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]