S. HRG. 106–864

ALZHEIMER'S DISEASE, PART 2

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS
UNITED STATES SENATE

ONE HUNDRED SIXTH CONGRESS

SECOND SESSION

SPECIAL HEARING

Printed for the use of the Committee on Appropriations

Available via the World Wide Web: http://www.access.gpo.gov/congress/senate

U.S. GOVERNMENT PRINTING OFFICE

63–945 cc WASHINGTON : 2001

For sale by the U.S. Government Printing Office
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ALZHEIMER'S DISEASE, PART 2

TUESDAY, MARCH 21, 2000

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 a.m., in room 216, Hart Senate Office Building, Hon. Arlen Specter (chairman) presiding.

Present: Senators Specter and Harkin.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Good morning, ladies and gentlemen. The hour of 9:00 having arrived, the Appropriations Subcommittee on Labor, Health, Human Services and Education will now proceed.

Our hearing this morning is on Alzheimer's disease. This subcommittee conducted the first hearing on Alzheimer's disease back in 1980, chaired at that time by Senator Tom Eagleton of Missouri. Today we continue the subcommittee tradition of focusing on this dreaded disease to consider the problems, to consider the prognosis, and to analyze ways to improve the condition of the some four million Americans who suffer from Alzheimer's, a dreaded disease which impacts the individual obviously, but the family and all those around him or her.

The statistics are foreboding for the future. Where we now have approximately 4 million Americans suffering from Alzheimer's at an annual cost of some $100 billion, the projections are as the baby boom generation ages that there will be 6 million sufferers of Alzheimer's by the end of the decade and 14 million by mid-century, and the cost will have ballooned to something like $375 billion.

The statistics are that 1 in 10 of individuals over 65 and 50 percent of those over 85 have Alzheimer's disease, which takes some 10 to 20 years before the symptoms begin to appear. Scientists have developed a vaccine which has promising aspects, and there is very intensive work being conducted by the National Institutes of Health on the issue.

Funding has risen consistently, starting in 1976 with $3.9 million, and the projection this year with the President's budget would raise it to $491 million, but that, in the opinion of Senator Tom Harkin, my distinguished ranking member, and myself, is insufficient. We have allocated very substantial additional funds to research in the National Institutes of Health by taking a sharp pencil, candidly, to other items on the subcommittee's allocation.

Three years ago we sought to raise the funding by a billion dollars, took the issue to the floor and lost 63–37, but we found $907 million by paring other accounts. Two years ago we decided that a billion was not enough and we decided to raise it $2 billion. Again, we lost on a floor vote, but again we made allocations from other accounts, because of our concern that NIH had that kind of priority, and added some $2 billion.

Last year we added $2.3 billion, again after losing a floor fight and again after reallocating the funds. This year Senator Harkin and I have filed a resolution calling for $2.7 billion on increase, and the budget committees are now meeting and have established a figure of some $596 million for all discretionary accounts, which will not leave this subcommittee with enough money to continue this juggling act to find $2.7 billion.

So one of the things that you, ladies and gentlemen, can do from all over the country is to identify those Senators who voted against increasing NIH and go to see them. We are going to make this a short hearing so you will have plenty of time to go see all the Senators on Capitol Hill and then to walk across the Rotunda and go visit all the House Members who have not been willing to provide that kind of funding.

My personal opinion is that the National Institutes of Health are the crown jewel of the Federal Government. In fact, I think they are the only jewels of the Federal Government.

One other item that I want to call to your attention, we are about to have a floor fight in the Senate on the use of stem cells for research. Stem cells are enormously helpful already in a number of ailments—on Parkinson's, on heart condition. They may be valuable for Alzheimer's. A stem cell replaces a cell in the body and is a veritable fountain of youth.

The controversy has arisen as to whether you can use embryos to extract the stem cells. The general counsel for the Department of Health and Human Services has handed down a legal ruling that Federal funds may be used on the stem cells once they are extracted from the embryos, but that makes it very difficult for research, and a concern has been raised on ethical grounds about using the embryos, but the only kind of embryos which are used are discarded embryos, embryos which cannot be used to produce human life on in vitro fertilization. If there were an issue of morality or use of these embryos for human life, I would never agree with that under any circumstance.

It is very similar to the battle we had over fetal tissue, on discarded fetal tissue, where for a long time that was not used medically, notwithstanding its great potential as a curative force. That battle has been won some time ago. When Senator Thurmond joined the forces in favor of use of discarded fetal tissue, the number of Senators who voted for it rose from about 40 to more than 80, and now we are going to have the battle over the stem cell issue, so I enlist your support on that as well.

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

Senator SPECTER. With those introductory remarks, we will now turn to our first witness, Dr. Richard J. Hodes, who is the Director

of the National Institute on Aging. Since 1993 Dr. Hodes has served in that capacity. He has also held other posts in the National Institutes of Health, including work on the National Cancer Institute, a program coordinator for the U.S.-Japan Cooperative Cancer Research Program and Deputy Chief of the Cancers Institute Immunology Branch, graduate of Yale University, and an M.D. from Harvard Medical School. It seems to me President Kennedy once had something to say about a person with degrees from both Harvard and Yale. You may proceed, Dr. Hodes.

Dr. HODES. Thank you, Mr. Specter, for this opportunity to appear with so many Alzheimer's disease advocates and to speak to you of the progress that researchers have made in understanding and developing interventions for Alzheimer's disease and to speak also to the urgency and opportunity for future research.

Senator SPECTER. Dr. Hodes, as you know, you have been here many times, our practice is to limit the opening statements to 5 minutes. Full statements will be made a part of the record. That will leave the maximum amount of time for questions and answers.

Dr. HODES. I will certainly do my best to meet with those time limitations. As you so adequately described, Alzheimer's disease is a progressive disease caused by abnormal changes in the brain which ultimately affect memory, cognitive function, personality, behavior, with devastating consequences for those afflicted as well as family members, loved ones, and society.

Tragically some 4-million Americans are currently affected with the disease, a disease which has an enormous age dependence. That is illustrated in the first poster which describes, much as you have summarized, the results of studies showing that the prevalence of Alzheimer's disease increases so dramatically with age until in the group 85 and over, some 47 percent or nearly half are afflicted.

This, combined with census projections for an increase in this vulnerable population 85 and over to some 20-million Americans at that age group at risk by the middle of this next century, create a really impending public health threat to us all.

In the face of that, NIA, NIH, the Alzheimer's Association are all committed to pursuing research aimed toward preventing these dire projected consequences. In the context of what we understand about Alzheimer's disease now, we can model its progression really into four stages. The first of these is that of the normal brain, with no symptoms and no lesions, which first progresses to presymptomatic Alzheimer's disease. That is the case in which there are no manifestations clinically but where we now understand there are changes in the brain.

The next stage is that of mild cognitive impairment, still not dementia, not Alzheimer's disease, but one in which symptoms of memory loss can be determined and in which again there is progression of certain detectable lesions in the brain, and then finally, the fourth, last stage, that of diagnosed Alzheimer's disease.

Until recently all interventions were directed exclusively at treating and attempting to slow the progression of already developed Alzheimer's disease. However, now armed with results of recent scientific discovery, we are for the first time able to attempt inter-

ventions prior to the onset of the disease in an effort to slow or prevent its progression.

With the recognition of our current opportunities, Congress recently provided us with language encouraging NIH to launch an Alzheimer's disease prevention initiative. The NIA, as the lead agency, is working with other NIH institutes, other Federal agencies, and important public and private partners such as the Alzheimer's Association.

This initiative has as its charge the intensification of basic research and the translation into interventions to prevent or slow the progression of Alzheimer's disease. In that effort, we recently last year were able to initiate the first large-scale prevention trial at NIA, one in which some 65 institutions will recruit individuals with mild cognitive impairment, that is, without Alzheimer's disease but at high risk to develop it, and will attempt to test the interventions in this case of vitamin E and Donepezil to see if they can alter the progression of the disease.

Similar studies will be undertaken looking at agents including nonsteroidal anti-inflammatories, estrogen, and a newly initiated study in collaboration with the National Center on Complementary and Alternative Medicine, a study to look at the effects of ginkgo biloba in that regard as well.

The clues for further discovery in Alzheimer's disease come from basic science. An example of basic science discovery in the past year which has really revolutionized and opened our eyes to further opportunities is illustrated in this transparency.

In contrast to what was the widely held belief until just the most recent years, it is possible in the human brain, and the brains of experimental animals as well, in adults, even older adults, for the brain to generate new cells. In the panel at the left, what the figure illustrates is that in young mice or in older mice there is a capability to generate new brain cells, and strikingly, as can be seen in the difference between those higher blue bars and the lower red bars, the rate of generating new brain cells, in fact, can be stimulated by in this case an enriched environment in which both physical and if you will intellectual challenges are posed to experimental animals, providing an intriguing model for the effect of such interventions in humans as well.

The figure at the right illustrates in those cells that appear green that even in the human brain, in fact, in adults, the generation of new brain cells can occur. This ability to stimulate, to provoke the generation of brain cells provides a new approach that will be translated in the future into interventions designed to either arrest or reverse some of the effects of Alzheimer's disease.

Similarly in other areas a convergence of both epidemiologic and basic science studies has provided us with new approaches to intervention. The next and last of the illustrations is the example for nonsteroidal anti-inflammatories.

On the left is an illustration from epidemiologic observations, indicating that those individuals who have a history of using nonsteroidal anti-inflammatories, such as Ibuprofen, for a variety of reasons have approximately a 50-percent reduction in the rate of Alzheimer's disease. So far, a correlation not demonstrated to be due to the causal effects of those interventions.

This observation is coupled, however, with what you can see on the right, a panel showing these networks of inflammatory cells surrounding Alzheimer's lesions. This convergence of evidence again will lead and has led to the initiation of studies to test the effects of such anti-inflammatories in preventing the development and progression of Alzheimer's disease.

Senator SPECTER. Dr. Hodes, did you say that there has not been a causal connection established?

Dr. HODES. That is right. It is important to note that when epidemiologic studies are carried out, they identify correlations or associations, in this case a strong association.

Senator SPECTER. Why do you not define an epidemiological study for our C-SPAN viewers?

Dr. HODES. I would be happy to. An epidemiologic study is one which examines in a population the behavior, the incidence of a given condition.

Senator SPECTER. Everybody in the audience knows it, but C-SPAN viewers may not.

Dr. HODES. What epidemiology is able to do is to track the correlations or associations—in this case to find whether there are particular factors which place individuals at greater or lower risk for Alzheimer's disease. Finding that people who have had a history of taking a drug such as anti-inflammatories had a lower risk of Alzheimer's disease means there is an association, but it does not prove that taking those drugs is what caused the decrease in Alzheimer's.

Senator SPECTER. What is the statistical base or evidentiary base for finding a lower incidence of Alzheimer's from those who take these drugs?

Dr. HODES. Well, the data shown here result from observations in the Baltimore Longitudinal Study on Aging which followed individuals over decades of their lives.

Senator SPECTER. Longitudinal study on aging?

Dr. HODES. That is right, in order to determine——

Senator SPECTER. What is a longitudinal study on aging?

Dr. HODES. A longitudinal study is one which follows the same individuals successively over time. That is the longitudinal dimension. So in this case some hundreds, now thousands of individuals have been followed for many years, in some cases many decades, so that it is possible to observe not just a cross-section, a snapshot of their condition, but changes that occur over time. In this case, including changes in cognitive function and in some the development of Alzheimer's disease.

Senator SPECTER. And by cognitive function you mean?

Dr. HODES. A variety of functions, the most commonly measured of which is memory in its various subtypes. The ability to recall, the ability to use recalled information as well.

Senator SPECTER. And you find from the observation of those people that there is an effect from the drugs?

Dr. HODES. Again there is a correlation, yes, which is——

Senator SPECTER. And correlation to what extent?

Dr. HODES. It means that if you take a look at people who have had a history of using these drugs and those who have not, that those individuals who have used the drugs, in this case, have only

half the rate of Alzheimer's disease compared to the individuals who have not had any such history of drug use.

Senator SPECTER. But that is not sufficient for you to come to a scientific conclusion of a causal connection?

Dr. HODES. It is not. It is suggestive and compelling data which has provoked the institution of direct, controlled clinical trials. In these trials, a group of individuals who do not have Alzheimer's disease but are at high risk to develop it are divided into two groups.

Senator SPECTER. What do you look for before you would move from suggestive and compelling to a causal connection, conclusion?

Dr. HODES. Well, the first step is to identify the correlative and basic science information, determine whether it has reached a critical mass so that it is sufficiently suggestive to warrant a clinical trial.

Senator SPECTER. A relative and critical mass. And by that you mean?

Dr. HODES. I mean that the judgment of expert scientists is applied to look at in this case epidemiological studies as well as basic science studies and determine whether they together are sufficiently compelling of a likely effect of the drug to warrant a direct test of that effect in clinical trial.

Senator SPECTER. So how much evidence do you need to come to a conclusion that there is a causal connection between the drug and the beneficial effect?

Dr. HODES. Well, to this point the gold standard, the most rigorous test that we can apply to that question is the controlled clinical trial. In a study such as this, a group of individuals who are at risk for disease are divided into two groups, groups that either receive the treatment being tested or some alternative—in this case a placebo, a sugar pill. The individuals do not know which group they are in, the physicians taking care of those individuals do not know which group they are in, and at the conclusion of the study, which involves following these individuals for months and years, there is a determination made of how many of those individuals have had a loss in cognitive function, how many have developed Alzheimer's disease, and only then does one uncode the results to see whether, in fact, the group that is involved in the active treatment, in this case anti-inflammatories, has had a reduced rate of development of Alzheimer's disease compared to the control group.

Senator SPECTER. Well, what are you looking for, again, before you would say that there is a causal connection? What level of proof?

Dr. HODES. Well, any differences that might arise from a clinical trial such as this are presumably due to the difference in what the subjects took—the drug or the control. Whether that test is a definitive one depends upon some very complex and austere statistical calculations, to make certain that at the level of high probability, that the difference in any groups that is seen is not due to chance but truly could have come only from the difference in the treatments for those individuals.

Senator SPECTER. I will try one more time. How high does the probability have to be before you say it is causal?

Dr. HODES. Well, I apologize for ourselves, scientists and statisticians, who answer those questions rather quantitatively. Traditionally if we can find——

Senator SPECTER. If you do that, I will apologize for us lawyers who ask the questions.

Dr. HODES. The results of studies can be analyzed. In a typical finding of a study to be interpreted to be positive, we say there is no more than a 100-to-1 chance that such a result could have occurred by coincidence alone, so the level of certainty in that case is at least 100 times that of a chance and coincidental observation.

Senator SPECTER. Dr. Hodes, when you run these tests and you give some people the real McCoy, and you give some people the placebos, by which you mean a sugar-coated tablet, so they think they may be getting something psychologically but they are really not, there is obviously a benefit for that group which receives the medicine. And I am sure you tell or perhaps I should ask you the question, do you tell everybody in the group that some will be receiving the medicine and some will be receiving placebos, so that they know that they may not be getting a medicine which would benefit them, but are just part of a test group getting a placebo which will probably do them no good?

Dr. HODES. You have addressed some extremely important points. And quite absolutely, it is ethically imperative that subjects who enter such a study understand precisely what the circumstance is and understand that they have a chance of receiving either the test medication or the placebo.

What I need to point out, however, is that somewhat in contrast to your remarks, that it is obviously to the advantage of those taking the drug to be in that group. The very rationale for carrying out these studies is one in which we simply do not know if the drug is effective or not. If we believe that we were withholding an agent that was known to be effective from one group, ethics would simply prevent us from conducting the trial. But generally as these trials are carried out we do not know if a drug will be effective. We even have to be open to the possibility it will have a negative or adverse effect, so the ethics are very important.

The patients are well informed. In the case of patients involved in studies such as these, both A, their families, their surrogates are also well informed of the nature of the study's design and are kept informed during the study of its outcomes as well.

I should add that we also monitor the trials, and as soon as it becomes evident, if it were to, that a given treatment is effective at a sufficient level of certainty, the study is then terminated. Certainly we would not continue to treat people in such a way as to withhold an agent of known effectiveness.

Senator SPECTER. How long does that customarily take? It can be a very protracted period of time, can it not?

Dr. HODES. It can. The length of clinical trials, of course, depends upon how quickly people who are not being treated develop the disease. In the case of Alzheimer's trials, the length of treatment is typically in the range of 1, 2, or 3 years depending upon the group and the rate of progression of disease.

Senator SPECTER. Dr. Hodes, is it possible to make a determination through gene testing as to whether an individual has an inclination or the risk of Alzheimer's?

Dr. HODES. In the past decade we have learned a great deal about the genetic influences on Alzheimer's disease, and it is important to distinguish there are a relatively small subpopulation of Alzheimer's cases, perhaps 10 to 15 percent, with what has been termed familial early onset Alzheimer's disease. In the case of that group there is a rather clear correlation between having a particular gene disposing disease and developing Alzheimer's. Again, I emphasize this is a very small subset, typically people who know they have a strong family history of the disease with early onset. In those cases genetic testing can identify individuals who are likely if not destined to develop the disease. However, for the great majority of cases, some 85 percent or so, there is no clear causal association.

There are, however, certain genetic types, alleles, ApoE4 is one that has received a lot of attention, which can increase the risk of an individual to developing disease, but the presence or absence in that case of that gene is not any guarantee that an individual either will or will not have the disease.

Senator SPECTER. Well, since there are some steps which can be taken, as you have described them, to treat Alzheimer's at an early stage, would you recommend that an individual undergo genetic testing to see if there is a proclivity for it, to get some help in advance to try to prevent it or slow it down?

Dr. HODES. This is a challenging, complex question that has received a good deal of attention and deliberation. In the instance of the nonfamilial Alzheimer's disease, current recommendations do not support the use of genetic testing, except in a research setting or in the hands of a physician as an adjunct to other diagnostic tests, but the simple determination that one does or does not have, for example, an ApoE4 allele in and of itself does not have sufficiently strong implications——

Senator SPECTER. ApoE4 allele?

Dr. HODES. Yes.

Senator SPECTER. Well, there are some people even in this audience who do not know what that means.

Dr. HODES. Yes.

Senator SPECTER. Would you define it?

Dr. HODES. Yes. ApoE is an abbreviation for, this will not help you a lot, I apologize, Mr. Specter, apolipoprotein E, which is a substance that was first identified to be important in carrying lipids, fats in the blood. Individuals, different individuals in the population have a different form or variation of this ApoE gene. One of those forms, ApoE4, is correlated with an increased risk of Alzheimer's disease. Individuals who carry that type compared to those who do not have in various studies a two- or three- or so-fold increase in the likelihood of developing the disease.

Senator SPECTER. Can you quantify the increased likelihood for developing Alzheimer's disease with ApoE4 allele?

Dr. HODES. Yes. If a series of individuals are typed to see whether they do or do not have the ApoE4 and then are studied for the likelihood of developing Alzheimer's disease, in certain popu-

lations—and it really does vary, it appears now, with which population one is concerned with—in certain populations there is a severalfold, in the range of 3- or 4-fold increase in the likelihood——

Senator SPECTER. Three or four times?

Dr. HODES. Yes.

Senator SPECTER. So why not test people? That is a fairly high incidence. If 1 person out of 10 over 65 gets it and if you find a three or four times likelihood—the whole field of genetic testing is scary, really. People test like they are getting their exams all at once, to find out what you have a risk of getting, and it is really in the beginning stages, but if there is a material chance of helping people not develop the disease or retard it, it seems to me that is something that people ought to be told about and at least have the option of doing. The recommendation may or may not be determinative, but that is a factor which I think could really stand some publicity.

What efforts are being made to publicize the availability of this kind of genetic testing to militate or to work against developing Alzheimer's disease?

Dr. HODES. Well, in fact, as I had mentioned, the particular issue of genetic testing and Alzheimer's disease was the subject of an extensive conference involving scientists, ethicists, which led to the recommendation that at the present time, given the incomplete state of our understanding of what causes the disease and what can be done to prevent disease, that the use of this genetic testing is appropriate only in the context of clinical trials or in association with other diagnostic measures being employed by a physician or caregiver. This is a situation which we clearly need to revisit constantly.

If we were, for example, to arrive at the point of having clearly demonstrable effective treatments to prevent the advance of Alzheimer's disease, then the imperative, the appropriateness for genetic testing to find out who was at a greater risk would certainly be reassessed.

Senator SPECTER. Dr. Hodes, when this subcommittee takes the lead in increasing the funding for the National Institutes of Health, we are constantly being questioned about how effective this increase in funding is. Are we increasing the funding too fast?

The funding for Alzheimer's has gone up in the last 5 years. In 1997 it was $329 million; in 1998, $356 million; 1999, $406 million—big jump there. And a bigger jump in 2000, $466 million. What has been the effect of this increase in funding? Is it worth it? What has been determined? What can you say which will persuade my colleagues in the Senate and the House that these substantial increases are producing some tangible results or the prospects of tangible results?

Dr. HODES. These increases, in the case of Alzheimer's disease research, have occurred at a time when scientific opportunities are expanding and have expanded at an unprecedented rate. Not only has basic science and discovery led to opportunities for interventions to treat and prevent, but it has now produced a generation of clinical trials which are exciting and are also extremely expensive. The kinds of trials that I have mentioned—that you will hear further commented upon this morning, designed to test the ability

of agents to prevent the development of Alzheimer's disease—require large numbers of individuals, trials that are expensive to conduct, but are the most critical hope for our finding a way to prevent or delay the onset of Alzheimer's disease.

Senator SPECTER. Well, scientists have developed a vaccine which appears to stop in the brains of mice the formation of these plaques. The enzyme has been identified implicated in the formation of the plaques. Can you give us any other specific results which have been achieved from this increase in funding?

Dr. HODES. Yes, I can certainly comment on those discoveries which you have mentioned. As you have said, in mice there is now an intriguing model in which immunizing against amyloid, the material that occurs in the plaques of Alzheimer's disease, can reduce those lesions in mice.

Now the process begins of looking to see whether those interventions will work and are safe in other animal models before ultimately considering their application to humans. As you have mentioned, some of the basic biology of what is responsible for causing amyloid plaques has been uncovered, so these two new enzymes that you alluded to, secretases, have now been shown to affect the production of amyloid in tissue culture or in vitro.

Now the critical determination is whether there are ways that one can intervene to block those enzymes and determine whether that will have an effect, both first in experimental animal model systems and ultimately whether they can be translated into clinical studies or interventions.

Senator SPECTER. Besides those items, can you specify other advances as a result of this increased funding?

Dr. HODES. The other major lesion that occurs in the brains of those individuals with Alzheimer's disease are the so-called Tau lesions or tangles. Only in the past year to two has it been identified both that mutations in Tau can be associated with disease in humans and that animal models can be generated to reproduce the effect of expressing abnormal Tau upon, generating a potential additional animal model for Alzheimer's disease.

In addition to this basic science, as we talked about prevention, the discovery of new ways to diagnose disease early has been critical. One of the areas in which progress has been made in recent years has been that of brain imaging. It is possible now in individuals who are not yet symptomatic with Alzheimer's disease to analyze the both function and structure of parts of the brain with now, suggestions being provided of changes in the brain of as-yet-asymptomatic patients which are predictive of a higher risk for developing Alzheimer's disease. That is critical both for understanding the process and for identifying individuals who are at the highest risk for Alzheimer's disease and who are candidates for interventions.

Senator SPECTER. May the stem cell research ultimately have some impact on Alzheimer's disease, in your opinion?

Dr. HODES. I think that the promise of stem cell research is extremely high, and there are many kinds of stem cells, as you alluded to earlier. The slides which I used to illustrate the generation of new brain cells in adults in effect are indicating the potential for stem cells already within the body, within the brain, to be

used, to be mobilized to generate additional and new functional brain cells. In addition, techniques for transplanting stem cells, neural stem cells, stem cells of other origin, are under intense experimental application at present as well.

Senator SPECTER. So stem cell research is being applied to Alzheimer's as well as other ailments?

Dr. HODES. It is.

Senator SPECTER. The Alzheimer's Association is looking for a $100 million increase. They would like to bring the figure up to $566 million. It is well known from the large group here attending, this is—this hearing coincides—this hearing was scheduled really to coincide with the 12th Alzheimer's Association public policy forum. We scheduled it for this purpose because everybody is in town today.

Give me your best reasoning why their request for $100 million would have a significant impact over and above what the President has recommended, which is only $491 million, $75 million less than the Association is looking for.

Dr. HODES. Well, we have clearly been able to make substantial progress with the budget allocations of past years, but I think it is also clear that the scientific opportunities are such that we have not been able to fund all of the meritorious and promising research that has been proposed to us by the scientific community. This includes the kinds of research which could be expanded with a yet additional budget increase, both in the basic science, where it is important to continue to discover the underlying causes, and to take advantage of those discoveries by funding additional what we call translational activities that involves ways to find better diagnostics early in the case of the disease to be able with techniques such as imaging to be able to uncover the disease.

It involves the ability to carry out more than one, two, or three clinical trials concurrently. At a time when the epidemiology and the demography point to the real threat of a burgeoning population with this devastating disease, we do feel this urgency to carry out clinical trials on as many fronts as are promising concurrently, simultaneously, to increase the probability that one or more of these will be successful in time to arrest disease for many of those at risk today.

Senator SPECTER. Five years ago we were told that about 28 to 34 percent of the grant applications were receiving awards, and even though we have increased the funding enormously, right at $18 billion now from less than $13 billion, we are told that still only about a third of the grant applications receive awards. That is because with the increased funding there are more people out there who are submitting grant applications, and that is good, but we have three doors, and we are only opening one of them on the grant applications.

Should we be giving awards to more? They are probably not all meritorious, but probably more than one out of three is meritorious. What would be the real funding level that you would like to see to make awards to all of the worthy grant applications?

Dr. HODES. Mr. Specter, to reinforce what you said, I can comment that last year the success rate at the National Institute on Aging was approximately 28 percent. This year, despite the sub-

stantial budget increases, it is estimated to be about 22 percent. At the level of the President's budget——

Senator SPECTER. You are making more grants, though?

Dr. HODES. Yes.

Senator SPECTER. There are more applications?

Dr. HODES. Well, yes. But both this downward trend and the projected decrease to 17 percent with the President's budget reflect both an increase in the number of applications, but at least as importantly, the increased average cost of these research projects. As I have mentioned, as we have the opportunities, the exciting opportunities to turn to clinical interventions, the cost of these studies also increases and has an influence on the proportion of grants that can be funded.

Senator SPECTER. How much money would you like to have for Alzheimer's research, Dr. Hodes?

Dr. HODES. Our professional judgment budget as expressed has proposed an increase in the range of some 15 percent, which is a range we would most appropriately like to see continue with continuity from year to year.

As I know you have heard in previous testimony, what is extremely difficult for the pursuit of science is to have an unstable base, an increase one year and none the next, and the fostering of productive science is certainly best accomplished with a consistent and reliable expectation of increase.

Senator SPECTER. Well, as long as Senator Harkin and I are here to make it bipartisan, you will get the increases.

Dr. HODES. Thank you, sir.

Senator SPECTER. If I had known that was going to be an applause line, I would have said it a lot earlier. Well, that is the question. You talk about 15 percent, and 15—I know your point on consistency, and I agree with it. We talk about 15 percent, all this goes through the Office of Management and Budget. So it is all pared down. The scientific views do not really come through OMB. Almost nothing comes through OMB. That is why we probe beyond that.

The current budget, Senator Taylor tells me, is $17.8 million. That is a lot of money but not necessarily a lot of money on a budget of $1,850,000,000,000. So the question comes back as to how many of those doors would you like to open. When you are dealing with a life and death, those are very high stakes. So we would appreciate your supplemental evaluation as to how many of those grants—you are now awarding only 22 percent, so 78 doors out of 100 are not being opened.

PREPARED STATEMENT

I would like to have the answer to specific questions. One is, how many of those other 78 doors ought to be opened, and what would it cost? Anything further, Dr. Hodes?

Dr. HODES. No. Thank you very much for this opportunity.

Senator SPECTER. OK, thank you.

[The statement follows:]

PREPARED STATEMENT OF RICHARD J. HODES

Mr. Chairman and Members of the Committee: Thank you for inviting me to appear before you today on an issue of mutual interest and concern, Alzheimer's disease. I am Dr. Richard Hodes, Director of the National Institute on Aging (NIA), the lead federal agency for Alzheimer's disease (AD) research. It is an honor to share with you information about the progress researchers are making to understand, treat, and prevent Alzheimer's disease.

If this hearing were being held ten years ago, the message would not be as promising. While there is still significant work to be done, the unprecedented pace of recent discoveries holds great promise for conquering this devastating disease. In the last decade, researchers have made tremendous strides toward solving the mystery of Alzheimer's disease, improving understanding of its underlying molecular processes, developing innovative diagnostic tools, devising effective treatments, and testing prevention strategies.

ALZHEIMER'S DISEASE: AN OVERVIEW

Alzheimer's disease, the most common cause of dementia among older persons, is the result of abnormal changes in the brain that lead to a devastating decline in intellectual abilities and changes in behavior and personality. AD eventually leaves patients unable to perform even the most basic tasks, with devastating consequences to individuals, families, and society. Scientists do not yet fully understand what causes AD, but it is clear that AD develops as a result of a complex cascade of events, influenced by genetic and non-genetic factors, taking place over time inside the brain with age being the most prominent risk factor. These events cause the brain to develop beta amyloid plaques and neurofibrillary tangles and lose nerve cells and the connections between them in a process that eventually interferes with normal brain function.

Tragically, as many as four million Americans[1] [2] now suffer from Alzheimer's disease, and an estimated 360,000 new cases will occur each year.[3] Research has revealed that the prevalence of AD doubles every five years beyond the age of 65, meaning dramatic increases in the number of new cases as the population ages. Being able to articulate the magnitude of Alzheimer's disease is a fairly recent development. In 1989, researchers working in East Boston completed a landmark epidemiologic study, which concluded that approximately ten percent of those over 65 and almost fifty percent of the community-based population aged 85 and older have possible Alzheimer's disease (Chart #1). This finding, coupled with current Census Bureau projections that indicate there will be 20 million people in the United States aged 85 or older by 2050[4] at risk for AD, makes Alzheimer's disease a very serious, impending public health threat. The NIH recognizes the urgency of this threat and is committed to supporting critical bench to bedside research, including basic, clinical, and behavioral research, to improve AD diagnosis, treatment, and patient care, and to delay, and eventually prevent, the onset of this devastating disease.

THE NIH ALZHEIMER'S DISEASE PREVENTION INITIATIVE

Advances in our understanding of AD in recent years have been substantial, including an enhanced understanding of the ways in which Alzheimer's disease develops. We can model the progression from normal function to clinically diagnosed AD through four distinct phases: (1) normal (no disease or symptoms); (2) pre-symptomatic (early brain changes, no symptoms); (3) mild cognitive impairment (memory deficit without dementia); and (4) diagnosed AD (mild, moderate to severe (Chart #2). Earlier clinical research efforts on AD focused on slowing worsening of symptoms among patients who had been diagnosed with AD. Armed with new knowledge, researchers, for the first time, are now developing and testing potential interventions to prevent the disease among persons with mild cognitive impairment and among those with no symptoms.

Capitalizing on scientific opportunity, Congress supported language in the fiscal year 2000 NIH appropriations report, encouraging the NIH to establish an Alzheimer's Disease Prevention Initiative. NIA, on behalf of the NIH, was asked to lead

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[1] Evans, D.A., *Estimated prevalence of Alzheimer's disease in the U.S.* Milbank Q. 1990;68:267–289.

[2] Advisory Panel on Alzheimer's Disease. Alzheimer's Disease and Related Dementias: Acute and Long-term Care Services. Washington, DC: U.S. Dept. Of Health and Human Services; 1996. NIH publication. 96–4136.

[3] Brookmeyer, R, Gray, S, Kawas, C., Projections of Alzheimer's Disease n the United States and the Public Health Impact of Delaying Disease Onset, AJPH, 88(9), 1337–1342, 1998.

[4] Bureau of the Census, Middle Series Projections, 1996.

this initiative and to collaborate with other Federal agencies, including other NIH Institutes (most notably, the National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, and National Institute of Nursing Research) and the private sector in its implementation. Later this month, the NIA once again will be chairing a meeting of the Ad Hoc Interagency Committee on Research on Aging, an organization comprised of almost 40 federal agencies interested in various aspects of aging research, to further discuss how the NIA may expand interagency collaboration of this important initiative.

The goals of the NIH AD Prevention Initiative are to: invigorate discovery of new treatments, identify risk and preventative factors, enhance methods of early detection and diagnosis, advance basic science to understand AD, improve patient care strategies, and alleviate caregiver burdens. The initiative is also focused on accelerating movement of promising new treatments and prevention strategies into clinical trials and improving understanding of normal brain function.

The NIA kicked off a major component of the AD Prevention Initiative last year by launching the first large-scale AD prevention clinical trial supported by the NIH, the Memory Impairment Study (MIS). The trial, which is being conducted at more than 65 medical research institutions in North America, including the 28 NIA-supported Alzheimer's Disease Centers, is evaluating vitamin E and donepezil (Aricept) over a three-year period for their effectiveness in slowing or stopping the conversion from mild cognitive impairment (MCI), a condition characterized by a memory deficit without dementia, to AD. Other ongoing or upcoming AD prevention trials will examine the effectiveness of naproxen and celecoxib, a Cox–2 inhibitor, (anti-inflammatory drugs), in reducing the development of AD, and whether treatment with a variety of agents, such as aspirin, vitamin E, antioxidants, or combined folate/B6/B12 supplementation can prevent AD. The effects of each of these agents on normal age-related decline will also be evaluated. In addition, the NIA is co-funding a new clinical trial with the National Center on Complementary and Alternative Medicine that is testing the effects of ginkgo biloba, a readily available natural product, to determine whether it can delay or prevent dementia in older individuals. Information about ongoing clinical trials and recruitment opportunities is available to the public through the NIA-supported Alzheimer's Disease Education and Referral Center web site (www.alzheimers.org) and toll-free number (1–800–438–4380).

IMPROVING DIAGNOSTIC TOOLS

Clinicians use a variety of tools to diagnose AD in patients experiencing difficulties with memory or other mental functions. These tools include patient history, physical exam, laboratory tests, brain scans, and a series of tests that measure memory, language skills, and other abilities related to brain function. However, at this time, AD can be diagnosed conclusively only by examining the brain postmortem. Yet, the tremendous progress that researchers have made in developing accurate diagnostic tests and techniques is making it increasingly possible for probable AD to be diagnosed at earlier stages. In specialized research facilities, including the NIA-supported Alzheimer's Disease Research Centers, clinicians can now diagnose AD with up to 90 percent accuracy.

The ability to assess the effectiveness of early treatments or interventions, such as those being tested in the AD Prevention Initiative, will be enhanced by our ability to observe brain function using new imaging techniques. In a recent study, investigators used magnetic resonance imaging (MRI) to determine volume measurements of the hippocampus, one of the regions of the brain responsible for memory function, in individuals diagnosed with mild cognitive impairment (Chart #3). Based on three years of observations, researchers found that in older people with MCI, the smaller the hippocampus at the beginning of the study, the greater the risk of developing AD later. This imaging study illustrates how abnormal cerebral function or anatomy could be used to aid in detecting the onset of AD before clinical diagnosis of AD, and how diagnostic advances can help ensure the effective application of emerging early interventions. Advances in imaging techniques also have important diagnostic implications for other neurodegenerative diseases, such as Parkinson's disease.

BENCH TO BEDSIDE: THE PATH FROM BASIC SCIENCE TO TREATMENT

Developing effective treatments for AD based on advances in basic research is a major focus of NIA-supported studies. The ability of researchers to conceptualize effective treatments was enhanced by the discovery of enzymes called secretases that are involved in the clipping of a normal cell surface protein to produce the amyloid peptide that forms the senile plaques found in the brains of AD patients. Identifying and understanding how these enzymes work will accelerate the development of

interventions to specifically block their action and stop the development of AD plaques. NIA will also support research to evaluate the potential of an immunization approach recently developed by researchers in the private sector, which, in mice, prevented the formation of amyloid plaques associated with AD.

Tau is a protein that is associated with the development of the neurofibrillary tangles characteristic of AD. A transgenic mouse strain that expresses a human tau gene and develops AD-like tau tangles has been developed. This model will help scientists understand how tau produces AD in the brain, and together with other AD models, will move researchers closer to developing effective preventive or treatment interventions. In another study, researchers demonstrated that shrinkage and dysfunction of certain brain cells that occur with age might be reversible. Researchers inserted into skin cells a gene that makes human nerve growth factor (NGF) and then injected the modified cells into the brains of experimental animals. After three months, the older animals injected with NGF-expressing cells had brain cells that resembled those of younger animals. Such gene transfer approaches to recovering cellular function could eventually have important implications for the treatment of AD and other chronic age-related neurodegenerative disorders in humans.

Another exciting advance with great promise has overturned long-held beliefs that cells of the adult brain cannot reproduce (Chart #4). Investigators have shown that rodents, non-human primates, and humans make new, mature brain cells, even in older adults, in the hippocampus, an important area of the brain for learning and memory. Intriguingly, the studies also showed that more new brain cells survived in mice exposed to stimulus-enriched environments than in those housed in a conventional laboratory environment for both young and old mice. Other research shows that stress can substantially reduce the production of new brain cells. These findings are major steps forward, opening the way to enhancing nerve cell development and to the possibility of replacing nerve cells lost through age, trauma, or disease.

The convergence of evidence from basic laboratory science and epidemiology studies has also led to the identification of candidate interventions that may treat or prevent AD. Chart #5 illustrates findings from an epidemiologic study in which it was observed that individuals who reported taking nonsterodial anti-inflammatory drugs (NSAIDS), such as ibuprofen, had a decreased risk of AD (Chart #5). In basic research studies, investigators have uncovered evidence that inflammation occurs in association with the lesions found in the brains of patients with AD, suggesting a possible role for anti-inflammatory agents in the treatment of AD. Similarly, both basic and epidemiologic studies have suggested a possible role for estrogen in protecting against development or progression of AD. Basic science investigators have observed the effect that estrogen can have on stimulating neuronal growth, and epidemiologists have observed an association of estrogen replacement use in post-menopausal women with a decreased risk of AD and enhanced cognitive function (Chart #6). As a result of these observations, the NIA is supporting studies to test NSAIDs and estrogen as potential treatments and preventative agents against Alzheimer's disease. These investigations include a multi-site study launched in 2000 to determine whether treatment with certain NSAIDs will slow cognitive and clinical decline in AD patients, and an ongoing study launched in 1999 to determine the effect of estrogen replacement therapy in preventing AD in women with a family history of the disease. The NIA looks forward to sharing the results of these studies with Congress and the public and, most importantly, to playing a role in helping translate the results of any promising basic and epidemiologic studies into effective, safe treatments for testing in clinical trials.

PROMOTING DRUG DISCOVERY AND DEVELOPMENT

The only currently FDA-approved treatments for AD are tacrine and donepezil. However, there are currently 50 to 60 drugs in the pipeline in various stages of testing that have shown promise in either treating the symptoms associated with AD or slowing the progression of the disease. The National Institute on Aging has developed ongoing programs to promote the discovery, development, and testing of compounds to alter (by reducing, slowing, or reversing) the cognitive and behavioral manifestations of Alzheimer's disease and eventually to delay the onset or prevent Alzheimer's disease entirely.

The NIA-supported Drug Discovery for the Treatment of Alzheimer's Disease initiative focuses on the preclinical discovery and development of novel compounds for the treatment of the cognitive impairment and behavioral symptoms associated with Alzheimer's disease. Potential therapeutic compounds require testing for safety in animals before moving into human studies. The NIA maintains a contract for funding investigators or small companies who have potentially interesting candidate

drugs but lack the means to begin the formal drug testing process to conduct animal studies to evaluate drugs for toxicity. If the toxicology screening is successful, the data generated can be used to file a request to the Food and Drug Administration (FDA) for approval to carry out initial tests for safety and efficacy in humans (Phase I trials).

Mechanisms have also been developed to facilitate human testing as illustrated by two recent program announcements issued by the NIA. The Alzheimer's Disease Pilot Clinical Trials Announcement supports smaller pilot clinical drug trials to evaluate dose, duration, recruitment strategies, and other related issues. The Alzheimer's Disease Clinical Trial Planning Grant supports planning for the development of larger multi-site studies once pilot data are available. Multi-site studies can be funded through regular research grants or through the clinical trials consortium supported by the NIA known as the Alzheimer's Disease Cooperative Study (ADCS).

The ADCS was established to support clinical trials on compounds which large pharmaceutical companies generally would not test. This category of compounds includes drugs which are off patent, or were patented and marketed for another use (but might be useful for treatment of Alzheimer's disease), or novel compounds from individual investigators or from small companies without adequate resources to underwrite clinical trials. The types of drugs that could potentially ameliorate symptoms and modify the disease process are varied but include, for example, antioxidants, anti-inflammatories, and compounds affecting estrogenic, neurotrophic, and neurotransmitter processes. The ADCS has stimulated numerous AD clinical trials, addressing treatments for both cognitive and behavioral symptoms. As a mechanism for translation of preclinical drug discovery results into clinical trials, the ADCS has, for example, done a Phase I safety study of a compound that stimulates the production of neurotrophins in the brain, which NIA supported through a grant awarded through the Small Business Innovative Research program and through preclinical toxicity testing supported through an NIA contract. The ADCS also conducts Phase II and III clinical trials (both treatment and prevention) of other compounds such as vitamin E, steroidal and non-steroidal anti-inflammatory drugs, estrogen, and melatonin for alleviating sleep disturbances. The ADCS has expanded the selection of drugs to go into clinical trials by calling on all neuroscience investigators supported by the NIA to identify drugs that may be tested in future ADCS clinical trials.

ALLEVIATING CAREGIVER BURDEN AND IDENTIFYING PATIENT CARE STRATEGIES

Perhaps one of the greatest costs of Alzheimer's disease is the physical and emotional toll it takes on family, friends, and other caregivers. According to a recent study that analyzed data obtained through the 1996 National Caregiver Survey, dementia caregivers spend significantly more time on caregiving tasks than do people caring for those with other types of illnesses and experience greater difficulties in terms of employment complications, mental and physical health problems, and caregiver strain than do people engaged in other types of caregiving activities.[5] While research on treating the root causes of AD is progressing rapidly, there is clearly a critical need to develop more effective behavioral and pharmacologic strategies to treat and manage problem symptoms in people who have AD and to alleviate caregiver burden. In response to this need, the NIH has made identifying patient care strategies and alleviating caregiver burden major goals of the NIH Alzheimer's Prevention Initiative.

As part of the AD Prevention Initiative, the NIA, in collaboration with the National Institute of Nursing Research, is supporting the Resources for Enhancing Alzheimer's Caregiver Health (REACH) initiative. This five-year, six-site intervention trial is testing the effectiveness of different culturally sensitive home and community-based interventions for families providing care to loved ones with mild and moderate dementia. These interventions include psychoeducational support groups, behavioral skills training programs, family-based interventions, environmental modifications, and computer-based information and communication services. Over 1,000 families are enrolled in the REACH study and approximately fifty percent are ethnically diverse (African-American or Hispanic). Recruitment for the first five sites was completed in 1999 and six-month outcome data will be available later this year.

In addition to the REACH initiative, NIA is also supporting research on special care units (SCUs), which are separate sections of nursing homes for residents with

[5] Ory, M.G., Hoffman, R.R., Yee, J.L., Tennstedt, S., Schulz, R. *Prevalence and Impact of Caregiving: A Detailed Comparison Between Dementia and NonDementia Caregivers,* The Gerontologist, 39(2), 177–185, 1999.

dementia. The idea behind SCUs is that people with dementia might benefit from specially designed programs or environments that differ from those in the traditional nursing home setting. The NIA has established a ten-site initiative that is examining the nature and effectiveness of SCU care in institutional settings, using cutting edge research methods. Best practices and effective interventions derived from the SCU and REACH initiatives, as well as other caregiving research activities, will be disseminated to the public through the NIA-supported Alzheimer's Disease Education and Referral Center, in collaboration with other federal, state, and local agencies involved in caregiving initiatives and the network of Alzheimer's Association chapters in communities across the nation.

The pace of scientific discovery in the area of Alzheimer's disease research, together with the energy generated by the Alzheimer's Disease Prevention Initiative, are grounds for excitement and optimism. The NIA recognizes that only through continued research will we thwart the inconceivable demands that unchecked growth of the population afflicted with AD would place on individuals, families, and society. Once again, thank you for your attention. I am happy to answer any questions you may have at this time.

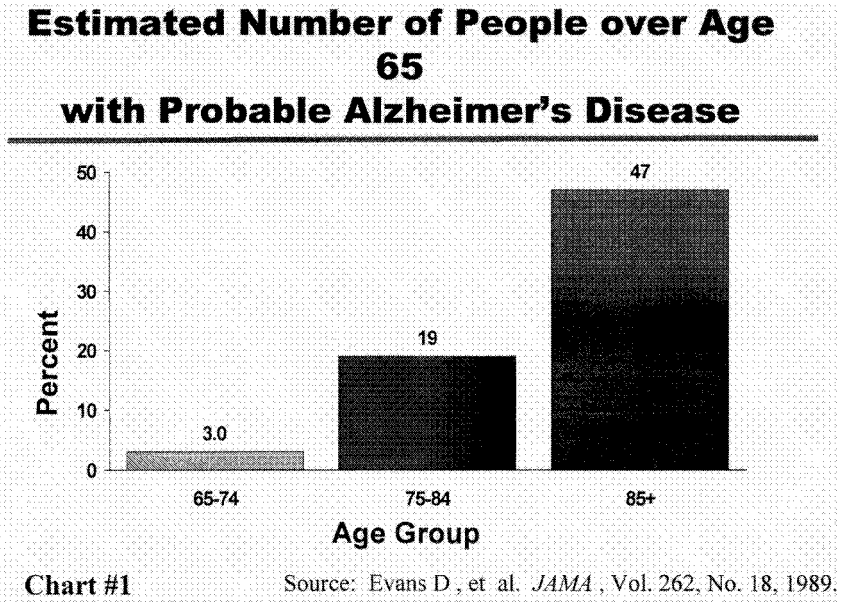


Chart #1 Source: Evans D , et al. *JAMA* , Vol. 262, No. 18, 1989.

Alzheimer's Disease Prevention Initiative

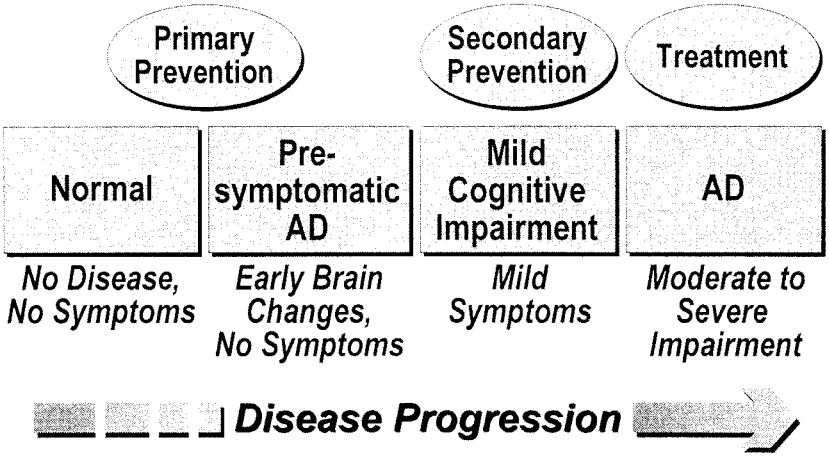


Chart #2

The Anatomy of Memory

Hippocampus Size in Aging and Alzheimer's Disease

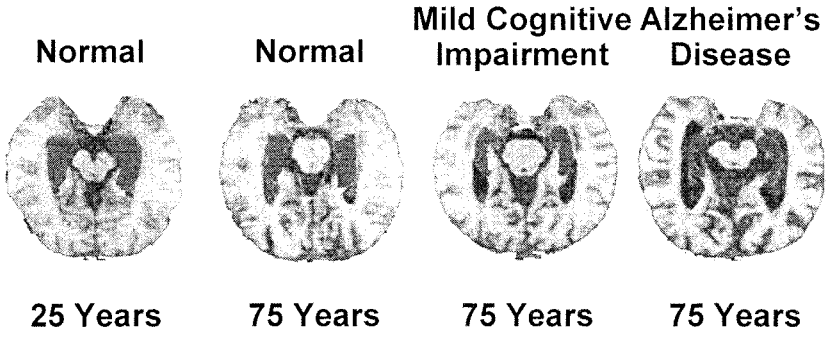
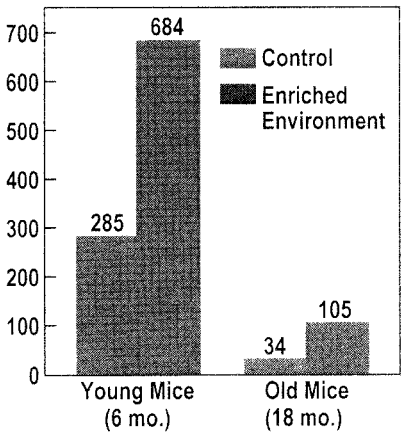
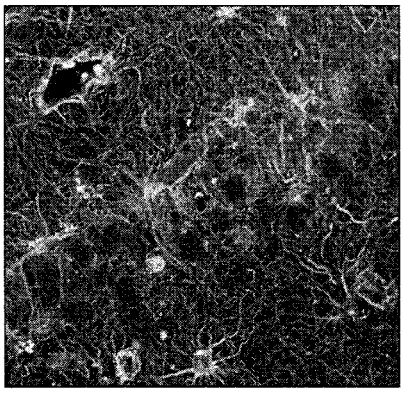


Chart #3

Growth of New Nerve Cells in the Brain



Effect of Environment and Age



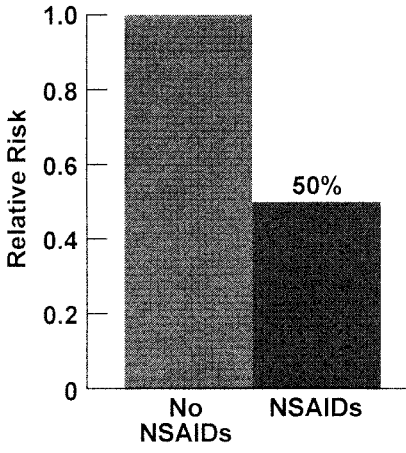
New Nerve Growth in Human Brain

J. Neurosci. 1998 18(9);3206-3212

Chart #4

Alzheimer's Disease and Inflammation

AD risk with use of NSAIDs



Signs of inflammation in the brain

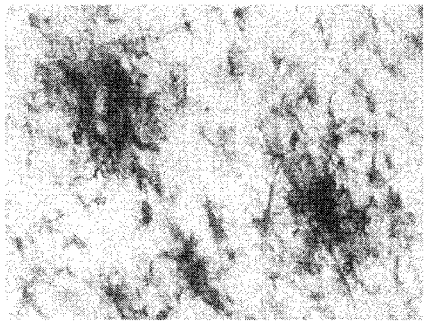


Chart #5

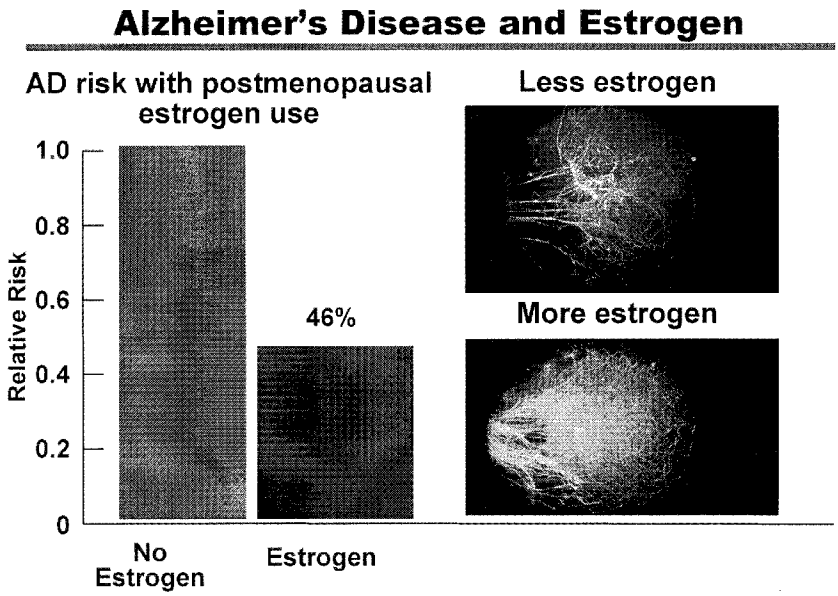


Chart #6

STATEMENT OF DR. STEVEN DeKOSKY, DIRECTOR, ALZHEIMER'S DISEASE RESEARCH CENTER, UNIVERSITY OF PITTSBURGH MEDICAL CENTER

Senator SPECTER. We will turn now to Dr. Steven T. DeKosky, a neurologist, Director of the National Aging Institute's funded Alzheimer's Disease Research Center, and director of the Division of Geriatrics and Neuropsychiatry at the University of Pittsburgh.

He chairs the National Medical and Scientific Advisory Council for the board of directors of the Alzheimer's Association. He also chairs the professional advisory board of the Greater Pittsburgh Chapter of the Alzheimer's Association, an M.D. from the University of Florida College of Medicine, an A.B. from Bucknell, and his number one credential is that he is the father of Allie DeKosky on my staff.

Thank you for joining us, Dr. DeKosky. We look forward to your testimony.

Dr. DEKOSKY. Thank you, Senator. Thank you for maintaining full employment in my household. It is a pleasure to be back before this committee. I was here 2 years ago to testify. I told you at that time that I was hopeful that we were getting answers that were going to be helpful in beating back Alzheimer's disease, hopefully in time for stopping what we see as a clear problem to come in the next several decades.

Based on what has occurred over the past 2 years, I am much more confident that we will get answers to how to slow down or stop this disorder. You have reviewed a number of the issues that I was going to present in my formal testimony. You have a copy of it, so I do not wish to go through it again other than to make a couple of points about issues that you covered with Dr. Hodes,

and also a couple which I think may be useful for the committee's deliberation.

We have developed a number of animal models which the scientists, of course, all love, and that we said we thought would be highly effective in letting us explain what happens as far as trying to stop the disease. Indeed, they have been very useful. The vaccination or immunization with beta amyloid of mice that shows what many people thought could not be done at all, that you could not only stop the lesions from forming in these mice but also actually have them regress, is clear evidence. And the phase one trials, the first trials for safety in humans using that immunization technique actually are beginning now at three different institutions around the country.

The chemicals or drugs that will suppress or stop the secretases, the biochemical scissors that cut this molecule in the wrong place and let amyloid form in the brain, are also about to enter phase one trials at several places around the country. And therefore although these are only safety trials, and that is first with respect to any of the drugs that we would use, it is pretty clear that we are at a point where even 2 years ago we thought was speculative.

The difference I think in why we would ask for additional funding now actually changes a bit. The kinds of studies that we will do for Alzheimer's disease and the reason that you are hearing about mild cognitive impairment or MCI, which is what we would describe as a recent memory function change in the absence of other changes of cognition, is because people who have that particular memory problem move to Alzheimer's disease at a rate—the number of people who have it per year—which is much higher than the rate of the normal elderly.

Somewhere between 12 and 15 percent of people will develop this disorder—if you identify it, they will develop Alzheimer's disease subsequently. What that means from the standpoint of how fast we can do studies, how quickly we can determine whether a medication works in slowing that progression down, represents an economic advantage and of course an immense advantage to our patients.

When we do studies, and I will use the ginkgo biloba study, which is the National Center for Complementary and Alternative Medicine plus NIA collaborative study, I am directing that study. That study will involve 3,000 normal elderly people who we will follow for 5½ years, to see whether ginkgo biloba will suppress the transition of people into either MCI or into Alzheimer's disease. That will take us 5½ years to get a yes or no, unless at 3 years when we do an interval analysis there is so clearly an effect of the ginkgo that we would stop the trial.

Now, the citizens of the United States pay approximately $100 million for ginkgo-related products. The Government wanted to know, is this helpful, and there are a number of scientific reasons why ginkgo itself might be helpful, but that study will take good volunteer, altruistic citizens of the United States who will agree to take either a placebo or this pill for 5½ years. They are all over 75, there are going to be difficulties getting them all into the clinic. These studies are going to take us time.

If we string them together 5 years at a time, based on our current restrictions of budget, by the time we string together two or three studies per year with respect to trying to slow the advent of Alzheimer's disease, we will already be into the middle of what is a huge demographic jump in the population at risk.

PREPARED STATEMENT

Our data suggests that if you take any one of those bars of millions and take 50 percent of it, those are the people, because this is the group at 85 and above, who will have Alzheimer's disease, and if you look at that target, which is ours for 2020 and 2040, those are the people that we have to be ready to address.

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

[The statement follows:]

PREPARED STATEMENT OF STEVEN T. DEKOSKY

Chairman Specter, Senator Harkin, Members of the Committee. It is a pleasure to be back. It was only two years ago that I came before you for the first time. I was hopeful then. I am confident now that we are getting the important answers we must have to effectively treat Alzheimer's disease.

We know a lot more than we did two years ago about the basic mechanisms of the disease and potential methods to treat or delay or prevent it. We have great momentum and synergy between the scientific and medical communities, which we must continue to support.

—We have a vaccine that appears to stop amyloid deposition in a mouse model of Alzheimer's disease, and safety trials of this vaccine in humans are underway.

—We have identified one of the two enzymes which initiate the formation of the characteristic plaques of Alzheimer's disease and are preparing to test inhibitors of this enzyme.

—We now have several animal models to model different aspects of Alzheimer's, including new ones that allow us to study the neurofibrillary tangles that are the other major hallmark of the disease.

—We have discovered that the brain has its own system for generating new neurons, leading to a novel potential therapy for Alzheimer's as well as other brain diseases.

—We have identified "mild cognitive impairment"—a defect in recent memory function, which is not yet Alzheimer's disease but has an increased probability of developing into Alzheimer's disease—a prime target for prevention.

We must maintain the current level of investment in Alzheimer research just to continue the basic science that will complete our understanding of the disease. But that will not be enough. Because we are in a race against time.

An estimated 14 million babyboomers are living with a sentence of Alzheimer's disease today. They will begin to turn 65 in 2010 and will enter the age of highest risk for AD about 2020. But we do not have that much time to find a way to prevent Alzheimer's disease. We know now that the disease process starts at least 10 years before these symptoms of the disease appear. Among those with mild cognitive impairment (MCI), 12 percent to 15 percent will convert to Alzheimer's disease each year. Within 5 years, half of those who now have MCI will actually develop full Alzheimer's disease. By that time, so much irreversible change in brain will have occurred that we will probably be able to do little about the further progress of the disease.

This means that our window of time to prevent Alzheimer's is very short. We have to find answers within the next 10 years, before the babyboomers start turning 65 and enter the age of risk. That is why we need an additional $100 million this year, just for Alzheimer research.

If Congress sticks with its commitment to double funding at the National Institutes of Health, and approves the $2.7 billion increase that you, Senators Specter and Harkin, are seeking this year, then we will have the money we need.

THE ALZHEIMER'S DISEASE PREVENTION INITIATIVE

Thanks to your additional investment in Alzheimer research over the past two years, the NIH—under the leadership of Dr. Hodes and the National Institute on

Aging—has initiated the Alzheimer's Disease Prevention Initiative. Now, at least four large scale prevention trials are underway. They are testing various promising compounds anti-inflammatory drugs, vitamin E, a current Alzheimer treatment drug, Ginkgo biloba, and estrogen to find out whether they can actually prevent or delay disease in people with mild cognitive impairment, or in those who have a family history of Alzheimer's but do not yet have any cognitive impairment.

These trials are expensive. They can cost as much as $15–25 million each. They take time—at least 4 to 5 years—to find out if the intervention makes a difference. And findings need to be replicated by at least one additional study before we can implement them in the population at risk.

If we spread out the money and do these studies one at a time, we will not find the answers in time. We must make the up-front investment in simultaneous trials now.

A MINORITY INITIATIVE ON ALZHEIMER'S DISEASE

Alzheimer's disease presents itself differently in particular ethnic and cultural populations. There are differences in risk factors, prevalence, family and community response; and the higher prevalence of diabetes and hypertension in some of these populations complicates evaluation and treatment. The Alzheimer's Disease Centers funded by the National Institute on Aging have opened satellite clinics to recruit a more diverse group of patients for our current research. But we need to do separate large-scale studies in minority populations to understand the impact of the disease and to discover novel, effective interventions.

One of the most promising areas for new research is the relationship between vascular disease and dementia. Vascular disease is the most common comorbidity in Alzheimer's. There is intriguing evidence that vascular factors may influence the clinical expression of Alzheimer's, and that hypertension may increase the risk of dementia. We need to pursue that evidence, but this too will take large-scale clinical and pathological studies in community-based populations, for which we do not now have the resources.

There is no area of scientific inquiry that holds more excitement or promise than the field of neuroscience, and Alzheimer research in particular. And there is no field that promises a bigger return on your investment. But we must act now. Time is running out.

On behalf of the entire scientific community, and the patients for whom we are trying to find answers, thank you for your continued leadership and commitment.

Senator SPECTER. Before going to questions, I am going to ask our other three panelists to join us at this time for their opening statements, and we will question them. Ms. Maureen Reagan, Mr. Frank Carlino, and Ms. Orien Reid. Would you join us, please.

STATEMENT OF MAUREEN REAGAN, MEMBER, ALZHEIMER'S ASSOCIATION BOARD

Senator SPECTER. We will begin with Ms. Reagan. Since 1999 she has served as a member of the board of the Alzheimer's Association, a well-known political analyst and radio and TV talk show host, an accomplished author. In her book "First Father/First Daughter" memoir, she outlined never-before-published anecdotes about her father, President Reagan. She has had several posts with the Republican Women, Republican National Committee, including cochair and special consultant to the chairperson for women's campaign activities. She also chaired a 36-member United States delegation to the 1985 World Conference of the United Nations Decade for Women. It is worth noting that in 1983 President Reagan signed a proclamation proclaiming the month of November 1983 as National Alzheimer's Disease Month.

Ms. Reagan, we thank you for joining us. We look forward to your testimony. And this may begin a little unusually, but I know this is a question on everybody's mind. How is President Reagan?

Ms. REAGAN. Well, thank you, Senator. He is doing very well, but the disease gets worse, and that is about the best that I can say

about it. I know that there is great concern on your part and many people's part when they ask that question, but I think there is also a little bit of glimmer of hope that perhaps we have been spared some of the ravages of this disease, but it is an equal opportunity disease, and it does not make special arrangements for former presidents or first ladies.

Senator SPECTER. Thank you for that comment and the insights into how he is feeling. Now we look forward to your testimony.

Ms. REAGAN. Well, thank you. As I said, Alzheimer's disease does not make special arrangements. We have over 500 family members here today on the Hill who are very anxious to tell their individual stories, and I speak for them as well as for my family. This disease is a thief that sneaks into the brain and robs a family of everything that is dear as it takes the loved one.

I am very grateful for Nancy Reagan. She is a model for caregivers throughout the country, and with the help of our good friend and nurse extraordinaire Diane, they make my father's days as stimulating and as fun as is possible to do.

It is very hard work for caregivers. I have talked with hundreds of them as I travel around the country. The emotional toll of losing a loved one and the 24 hours a day that it takes to care for them is really quite devastating when you realize that most caregivers are older themselves, and they have their own health problems, which are many times left uncared for because of what they are doing for their Alzheimer's patients. And that is why it is very important, in addition to research, that we look at ways to provide more support for caregivers with the caregiver tax credit and with grants to states and communities for respite care and day care that can help the patient as well as the caregiver.

As you said, in 1983, my father offered his proclamation, and he did it because this is a relatively unknown disease. It has stricken millions of people, and he felt it was time to pay attention to that. But even more important, in 1994, when he wrote his letter to the American people, told them that he had this disease and that he knew what was coming, he made it all right to talk about it.

He brought it out into the open, and he caused light to shine in the lives of families who had dealt quietly and very much alone, and between his letter and the fact that the Alzheimer's Association over the last 20 years has worked so hard to bring attention to this disease, I think he has always been my hero, but never more so than when he did that.

If he were sitting here today, Mr. Chairman, I know that my father would commend you and the members of this subcommittee for going beyond talk and increasing substantially the investment in research. Because of that investment, scientists are able to unlock the basic mechanisms of Alzheimer's disease and to offer hope to generations in the future. I encourage you to continue this support. I hope that our arguments today will benefit you as you go forward to talk to the rest of your colleagues because even if we were to come up with a way to end this disease today, there would still be four million—or to prevent it, there would still be over four million Americans like my father who would still need care. So we need to examine both sides, not only how we prevent the disease but how we deal with those people who are suffering.

PREPARED STATEMENT

So for my father and for Nancy and for all the individuals and caregivers across America who are praying for help, I plead with you to redouble our efforts. We must be the last generation of American families to deal without hope. Thank you, Senator.

Senator SPECTER. Thank you very much, Ms. Reagan. We obviously wish your father the very, very best.

Ms. REAGAN. Thank you.

[The statement follows:]

PREPARED STATEMENT OF MAUREEN REAGAN

Mr. Chairman and members of the Subcommittee: My name is Maureen Reagan and I am here to speak for my family and for millions of families who are struggling with Alzheimer's disease.

The first question on your mind is, "How's my dad doing?" I am asked that question wherever I go. I suspect out of a sincere concern for my father, but also, I think, out of some heartfelt hope that maybe he and Nancy are being spared in some small way from the ravages of this terrible disease.

Well, I have to report to you that Alzheimer's disease doesn't make special arrangements for President's or first ladies or anyone else for that matter. When it takes hold it follows its own course of destruction, frequently ravaging not only its direct victim, but also the caregivers and loved ones along with it.

This disease is a thief that sneaks into the brain and robs its victims of so much of what is precious about life our memories and our experiences, ultimately life itself.

I thank God for Nancy and the wonderful care she gives my dad. And, I thank God again for sending Diane, a nurse-extraordinaire. They are quite a team and he couldn't be better cared for. They, like millions of caregivers, make sure his days are as stimulating and fun as possible.

But, it is hard work for caregivers. I've talked with hundreds of them as I travel around the country. The emotional toll of losing a loved one to this disease is wrenching. And, most caregivers are themselves older and, therefore, have their own physical limitations that are compounded by the enormous stresses of caregiving. We are fortunate in my family that we can afford help. Without it, this disease would be truly overwhelming. But, many families, for financial and other reasons, attempt to do it alone, or help simply isn't available. That's why you must enact some relief for caregivers this year.

My father has always been viewed as a person with vision; someone who has the uncanny ability to see, in an unfiltered way, where we as a nation are and where we ought to be. More than sixteen years ago on September 30, 1983 he issued a Presidential proclamation that for the first time drew national attention to Alzheimer's disease. He was moved to do this, in large part, because this relatively unknown disease had stricken millions of families; yet most Americans had never heard of it. In that proclamation he wrote that, "The emotional, financial and social consequences of Alzheimer's disease are so devastating that it deserves special attention."

And then in 1994 when the disease found its way into his brain, he had the courage to issue another kind of proclamation in the form of a very personal letter to the American people. My father has always been my hero, but never more than when he took that courageous stand, thereby drawing attention to, and making it alright to talk about, this awful disease. But talk isn't enough. We must do something about it.

If he were sitting here today, Mr. Chairman, I know that my father would want to commend you and this subcommittee for going beyond talk and increasing substantially the investment in research. Because of that investment, scientists have been able to unlock the basic mechanisms of Alzheimer's disease, offering hope to generations in the future. I encourage you to continue that support for research and to add to it support for caregivers. Because even if we were to come up with a way to prevent this disease tomorrow, more than 4 million Americans, like my dad, will still be in need of care.

So, for my father and Nancy and all the individuals and caregivers across America who are praying for help, I plead with you to re-double your efforts this year. We need you to increase the research funding on Alzheimer's by $100 million. We need you to fund caregiver support programs. And, we need your courage and stead-

fastness, not only this year, but in years to come to help bring this disease to its knees. We must be the last generation of American families to live without hope! And with your help we will be.

Senator SPECTER. We will do our best, as we said before, to keep the funding coming and to try to work for the future. There are many people who want to come in. If you come to the far wall on this side, you are welcome to come in, if you move around and those on this side can move farther up here. You can even take some of the chairs. We will not have all those chairs filled. Be senators for a morning. Come on up. We want everybody who is in the hallway to gain access to the room. We have been joined by our distinguished Ranking Member, Senator Harkin. Tom.

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. Thank you, Mr. Chairman. I apologize for being late. We always have 10,000 things to do around here, but I did want to be here because of my long-time interest in this issue and because of the need to continue our efforts together.

I just said to our chairman when I walked in, I said I heard a lot of clapping when I came around that corner down there, and I wanted to know what that was all about.

Senator SPECTER. I told him that I mentioned his name.

Senator HARKIN. So I learned that my friend and distinguished chairman had said that we are going to continue a very strong bipartisan effort to get a doubling in for the National Institutes of Health. I just wanted to let you all know that I am in lockstep with him on this, and we will do everything we can to ensure that that happens and to make sure that we keep up the funding.

I just ask that my statement be made a part of the record. I, too, want to join in wishing your father the best. You know, it really, because of who he is and because of his great life and the leadership he gave to this country, it really has brought home that Alzheimer's can hit anyone. It is not just someone maybe that did not take care of themselves. Your father was always the picture of health, I mean always the picture of health. And so I think it just brings home that no one is immune, no one, not anyone is above it, and that we really have to focus on this.

PREPARED STATEMENT

I just would just say, Mr. Chairman, again along with you, I thank you for your leadership in this area. There are great breakthroughs being made. I am convinced, as I have watched the progress in areas like stem cell research, that I really believe that in a very short period of time we are going to be able to have interventions that will put off the onset of Alzheimer's. If we could just put it off for 5 years, they would tell me we would save almost $50 billion a year, just by putting it off for 5 years, so hopefully within the next few years we will have those interventions, and the next step, of course, is reversing it and finding a cure. To that end, I am sure we are all committed, and again I thank you all for being here. Mr. Chairman, again thank you for your leadership.

Senator SPECTER. Thank you very much, Senator Harkin. Your full statement will be made a part of the record.

[The statement follows:]

PREPARED STATEMENT OF SENATOR TOM HARKIN

Mr. Chairman, I want to thank you for having this hearing today and thank our distinguished panel for sharing their testimony with us. I also want to welcome the many volunteers with the Alzheimer's Association who have come to Capitol Hill today to advocate for more funds for Alzheimer's research and care giver support—and, in particular, I want to welcome the delegation from Iowa. I know you have your hands more than full, so your willingness to travel here is even more admirable. I want you to know, you are making a difference.

I have had the privilege of visiting with and listening to Iowa families struggling with Alzheimer's and the high costs of health care. This disease takes a tremendous and terrible toll on families—it also takes a tremendous and terrible toll on family budgets.

I believe we can invest smarter to help ease the burden on families and save taxpayers at the same time. That's why Senator Specter and I are fighting so hard to increase our national investment in medical research. Nearly $100 billion a year is lost to the economy each year because of Alzheimer's. But if we were to just delay the onset of Alzheimer's's by five years, we could save as much as $50 billion a year.

Today, about 15 percent of the Pentagon's budget goes to research & development. But less than 3 percent of our health dollars are invested in research. Pentagon research has paid off. It's time to invest in a smart bomb to wipe Alzheimer's off the face of the earth. By investing more in research we can save money and save lives. And in the meantime, we also need to do more to help care givers cope with the tremendous stresses and costs of Alzheimers.

Thank you, Mr. Chairman and I look forward to hearing from our witnesses.

STATEMENT OF ORIEN REID, CHAIRMAN, ALZHEIMER'S ASSOCIATION BOARD

Senator SPECTER. We now turn to Miss Orien Reid, elected as chairman of the national board of directors of the Alzheimer's Association November of last year. She was a primary caregiver for her mother who died from Alzheimer's disease in 1992. She spent 26 years as a television and radio consumer reporter in Philadelphia, where I got to know Orien on a personal basis. Began at KYW news radio and most recently at WCAU-TV. Currently owns her own media consulting business. A master's from Atlanta University School of Social Work and her BA from Clark College. Thank you for joining us, Ms. Reid.

There are still some more chairs up here for people who want to sit. We welcome you five ladies to the Senate panel.

Ms. Reid, the floor is yours.

Ms. REID. Well, thank you, Senator Specter and Senator Harkin. A couple of years ago, as you mentioned, I came here as a caregiver to speak for my mother and my grandmother, my aunt, and my uncle, all of whom had Alzheimer's disease, and also to speak for my children, who are just simply terrified that this killer has just not let our family go yet, but today I am speaking as the chair of the Alzheimer's Association.

I speak for our 200 chapters, for the 4 million people who have Alzheimer's disease now, and their families, and for the 14 million baby boomers, of whom I am a part, who are going to get this disease if we do not do something very soon.

We are here to thank you today for your commitment and your enormous effort in helping us to fund research to end this disease, and I also want to submit a copy of the Association's national public policy program to conquer Alzheimer's disease. Today you have 500 people who are here who are going to be taking this document personally to their Senators and Representatives to tell them about our program to end Alzheimer's disease.

Our first priority is research. Your proposal is just outstanding for $2.7 billion to increase the NIH's budget so that we can get—we believe we need $100 million to fight Alzheimer's disease. I am not a scientist, and I would not presume to present even more evidence than has been presented by Dr. Hodes and Dr. DeKosky, but I can add for you a very personal note.

For each of us in this room and for anyone who has ever been touched by Alzheimer's disease, Senators, we are simply in a race against time. Would you believe that today I am only 15 years younger than my mother was when she received the sentence for Alzheimer's disease, and the researchers say that if I am going to get this disease when I reach her age, the molecular mischief has already begun in my brain. I just do not have any time to spare.

In the 8 years that I have been involved with the Alzheimer's Association, I have heard scientists change their message from one of cautious optimism to, at best, to outright certainty that we can end this disease, but only if we have enough resources to do it.

The agenda for research is very clear, as you have already heard from the experts. We need the additional $100 million to launch the kinds of prevention trials that Dr. DeKosky talked about. We also need to finally start a minority initiative on Alzheimer's disease. We need to make sure that we are developing the kinds of diagnostic tools and the kinds of interventions that work for everyone and not just for one particular population.

We know we do not have to persuade you because you are already on our side, and you understand this, but our job is to convince your colleagues. We will be talking to some of the members of the other committees who are responsible for Medicaid and Medicare funding, and we will show them how the future of these two programs directly depends on our success to end Alzheimer's disease.

Medicare spends 70 percent on average more for health care for a beneficiary with Alzheimer's. Medicaid spends 65 percent more, and 22 percent of the dual eligibles, those on Medicaid and Medicare, are folks with Alzheimer's disease. So our message to your colleagues is very simple. There is no way that you can save Medicare and Medicaid unless we bring Alzheimer's disease under control, and we can only do that through research, and for baby boomers like me, and like you, Senators, there is an increased sense of urgency.

Briefly, there are two other important issues that we feel are so very important. We urge you to appropriate $25 million this year for Alzheimer's demonstration grants. I have already handed in my written testimony. It describes how effective this has been for 15 communities where actually they have changed the way they can deliver services to people with Alzheimer's disease.

We are also asking for support for the family caregiver support program, and we are asking for funding this year.

PREPARED STATEMENT

Mr. Chairman, I know that you have lots of priorities that you have to balance, and we appreciate that, but when we look to the future, we must find a way to end this disease, so I thank you for all of your support, for all of your efforts. And for all of the people

in the Association and for my children and my grandchildren, I thank you.

Senator SPECTER. Thank you very much. Thank you very much for those very touching and profound remarks.

[The statement follows:]

PREPARED STATEMENT OF ORIEN REID

Thank you, Senator Specter and Senator Harkin for holding this hearing and inviting me today. Several years ago, I came here as a caregiver to speak for my mother, my aunt, my uncle, and my grandmother all of whom had Alzheimer's disease. And to speak for my children, who are terrified that this killer is not finished with our family yet.

Today, I am here as Chair of the Board of Directors of the national Alzheimer's Association. I speak for our 200 chapters, the 4 million people who have the disease now and their families, and the 14 million babyboomers who will get Alzheimer's if we do not stop it soon.

I would like to present to you the Association's National Public Policy Program to Conquer Alzheimer's Disease. Today, 500 Alzheimer advocates from across the country will deliver this National Program personally to their own Senators and Representatives.

We are here to thank you for your constant leadership on issues that matter to the Alzheimer community, and to tell you that we are behind you in your continued efforts to increase funding for Alzheimer research and services.

As you know, the Alzheimer's Association is the only national voluntary agency dedicated solely to this terrible disease. Our mission is to create a World Without Alzheimer's Disease while we support the families who must deal with it today. We know that you share those goals and, with your help, we will accomplish them.

Our National Program calls on Congress to act in 3 areas: research, Medicare, and long term care. We know that some of these issues fall in the jurisdiction of other Committees. We are here to talk to you about those issues that are before this Subcommittee.

Our first priority is adequate funding for Alzheimer research. Your proposal for a $2.7 billion increase in overall funding at NIH this year the next step in your efforts to double funding within 5 years is absolutely essential if we are to find the additional $100 million that we need for Alzheimer research.

I am not a scientist and would not presume to add to the persuasive scientific arguments that the researchers are presenting at this hearing. But I can make a very personal plea, for each of us in this room and for every family that has been touched by Alzheimer's disease. We are all in a race against time. Right now, I am only 15 years younger than my mother was when she received her sentence of Alzheimer's disease.

The researchers say that if I am going to get the disease by the time I am the age she was, the "molecular mischief" in my brain has probably already begun. I do not have any time to spare.

In the 8 years I have been involved in the national Alzheimer's Association, researchers have changed their tune. They are no longer "cautiously optimistic." They are confident that we can master this disease—if we have the resources to do so. The agenda for research is clear, as you have already heard from the experts. The additional $100 million will provide the resources for two urgent priorities.

—First, for the Alzheimer Prevention Initiative to accelerate the expensive large scale clinical trials that will prove which treatments work to prevent the disease, and to develop the techniques for early diagnosis to make sure that those treatments get to the right people, in time to make a difference.

—Second, for a Minority Initiative on Alzheimer's Disease. By 2030, 25 percent of the aging population will be non-white. Alzheimer's differs in these population groups, and a common condition among minorities hypertension may increase the risk of dementia. We must start the studies now to understand the impact of the disease in diverse populations, to determine the relationship between vascular disease and dementia, and to discover effective interventions.

For your colleagues on other Committees who are responsible for the future of Medicare and Medicaid, we will make the argument that the future of these programs will depend directly on our success in slowing the progress of Alzheimer's disease. We already know from the Health Care Financing Administration that Medicare spends 70 percent more on average, for a beneficiary with Alzheimer's disease. Now, a new study from Pennsylvania shows that Medicaid long term care costs 65 percent more for a beneficiary with Alzheimer's disease.

There is no way to save Medicare and Medicaid if we do not bring Alzheimer's disease under control, and we can only do that through research.

The second matter before your Committee is funding for Alzheimer services. Since 1992, you have funded small grants to states as little as $250,000 each—that are changing the way Alzheimer families receive the services they need. The projects focus on underserved ethnic and cultural minorities and rural communities. Let me give you a few examples of the innovations your investment has brought in the states that have been lucky enough to get the 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.

—Small towns in Georgia that cannot support a full time adult day care center are now served by a mobile dementia day care program.

—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.

—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.

Annual appropriations for this program has never exceeded $6 million. That has been enough to fund only 15 projects, although more than 40 states applied for the money. This year, the Administration on Aging is seeking new competitive grant applications. We expect most states to submit proposals. We urge you to appropriate $25 million to allow these innovations to go forward in every state that submits a qualified proposal. 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 again.

Finally, may I say just a word about the broader issue of caregiver support. I realize this is not the topic of today's hearing. But I want to make clear that the Association supports the proposals before Congress that would support all caregivers, whether they are dealing with Alzheimer's disease or another devastating illness or disability. A $3,000 tax credit and a $125 million appropriation for a family caregiver program—proposals that have strong bipartisan support—are important steps you can take now to shore up the families who are the invisible care system in our country.

Mr. Chairman. We know there are competing priorities before this Subcommittee, and we understand the fiscal constraints under which you must try to balance those priorities. But as we look to the future, the case for a frontal assault on Alzheimer's disease 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 our children and grandchildren, thank you.

STATEMENT OF FRANK CARLINO, ALZHEIMER'S PATIENT

Senator SPECTER. We turn now to Mr. Frank Carlino, a resident of Cornwall, New York. In July of 1998, at the age of 58, Mr. Carlino was diagnosed with early onset Alzheimer's disease.

Prior to falling victim to Alzheimer's disease, he operated his own architectural consulting firm. Currently taking part in an early onset support group organized by the Mid Hudson Chapter of the Alzheimer's Association. Received his architectural degree from Pratt Institute in New York. Thank you for joining us, Mr. Carlino, to share with us your experiences.

Mr. CARLINO. Thank you very much, Senator Specter and Senator Harkin, for giving me the opportunity to be here and to represent my 4 million fellow Alzheimer's sufferers.

You have my written testimony, so I would like to speak to you from my heart. Alzheimer's has taken a life, a pleasurable life. I have been married for 40 years to a most wonderful woman, my wife Elizabeth, who is the wind beneath my wings. I have 4 wonderful children and 13 grandchildren.

We enjoyed a terrific life, and then the bottom fell out. I had my practice for close to 30 years, and I lost it because I was not able

to think properly. Not knowing that I had early Alzheimer's, I was able to take a job with the consulting firm, the Archdiocese of New York, and I lost that because I could not perform. It was then that I found out that I had early Alzheimer's.

In the meantime, between losing my business and so forth, I got into considerable debt, and my wife is now the principal breadwinner. Speaking through the eyes of someone with Alzheimer's, it is devastating, because I can no longer provide. To make matters worse, I get put in a Catch–22 situation, Senators, where the Government tells me, well, you are 100 percent disabled, therefore you cannot work, you cannot earn any more than $200 a month, so sit on the couch and enjoy life, what is left of it.

PREPARED STATEMENT

All this has been taken away. You asked the doctors before what you can do to justify the expenditure before your colleagues. Please, Senators, take them my message. My life is slipping away. They have the ability to save it. They are the life preserver. I am drowning. Save me, please. God bless you.

[The statement follows:]

PREPARED STATEMENT OF FRANK CARLINO

Thank you very much Senator Specter and Senator Harkin for giving me the opportunity to testify. I am honored to be here.

My name is Frank Carlino and I am from Cornwall, New York. I have been married to my wonderful wife, Elizabeth, for 40 years. We have been blessed with 4 terrific children and 13 amazing grandchildren.

I was diagnosed with early onset Alzheimer's disease in July 1998. At the time, I was 58 years old. Although Alzheimer's disease primarily affects older people, an increasingly large number of early-onset patients are in their 40's and 50's.

I am aware that on the outside, it does not appear that there is anything wrong with me. In fact, I may even look like someone you know—a friend or neighbor or even a colleague. But I have a disease that is slowly destroying my mind. I am here today to tell my story and to thank you for your steadfast leadership on Alzheimer issues.

My story actually began almost a decade ago. In the early 1990's, I began to have trouble doing ordinary tasks and I started making mistakes at work. At the time, I had my own architectural firm. I employed 12 people full time but I was struggling because the economy was bad and the country was in a recession. As a result, there was very little work available in the community and I was worried that I would have to lay off some of my staff. I was under a tremendous amount of pressure and my mistakes became more frequent. I managed to come up with a variety of excuses for my poor performance—stress, anxiety about the future, concern for the welfare of my employees, etc. I figured that I was just going through a rough patch and that things would correct themselves over time.

The recession ended, the economy turned around and my firm began to send out proposals and bid on jobs again. Although I would send out 25 proposals a week and we were bidding on as many jobs as possible, we still weren't getting any work. It was only after I was diagnosed that I realized why almost all of our proposals were rejected. They were a mess! I had submitted poorly organized proposals and bids that were full of spelling errors and grammar mistakes.

As my business continued to fail, I was approached by the Archdiocese of New York and offered a job as an architectural consultant, covering a 60 parish territory. I closed my practice and went to work for the Archdiocese. Although I was devastated by having to close my business, I was relieved to be getting out of that high-pressure situation.

At first, I was doing well in the new job but then I began having trouble. I missed appointments, couldn't finish assignments and began getting lost in communities that were familiar to me. My supervisor became aware of my missed appointments and poor performance and about 18 months after I started, he called me into his office and suggested that I see a doctor about my problems. He told me that if I

had a medical problem I could go on disability but that if I didn't get checked out, he would have to let me go because I couldn't handle the job.

I saw my family doctor immediately who referred me to a neurologist. I had a complete medical work-up including an MRI, many blood tests and a memory test. Within 3–4 months the diagnosis was complete—early onset Alzheimer's disease.

Overnight, my life was turned upside down. I lost my job and went on disability. I was declining very rapidly so my neurologist suggested that I begin taking Aricept. I noticed an almost immediate improvement after I began taking the medication. I could function again and complete tasks. I felt like I was starting to get my life back. I am still on Aricept and I honestly believe that it has slowed the progression of my disease. But I know it won't stop the inevitable.

As an architect, I could do algebra and geometry in my head and calculate complicated dimensions for high rise buildings with ease. In high school, I got an almost perfect score on the New York state math exam. Today, I can't balance my checkbook. After high school, I spent three years in the Army in a Special Operations unit. Everything had to be committed to memory. I can't memorize five items on a shopping list now.

Alzheimer's disease prematurely ended my career and destroyed my financial security. It will steal my memories and eventually it will rob me of my independence but I will not let it take my spirit. Instead of dwelling on what I have lost, I am focusing my attention on the activities I can still enjoy. I am a deacon in my church. I participate in a wonderful early-onset support group organized by the Alzheimer's Association Mid-Hudson Chapter. There are 5 of us in the support group and we have become great friends. The support group has also been a great resource for my wife. I still drive although I have an agreement with my doctor that I will not drive anywhere that is more than 25 miles from my home. I keep maps of places I go on a regular basis, like the doctor's office or the hardware store, in my car. I am perhaps one of the few men in this room who will not hesitate to ask for directions! I am also in the process of converting a New York City transit bus into a motor home that my wife and I are planning to take on weekend camping trips. The project is nearly completed and it has given me a tremendous sense of satisfaction.

While I am still able, I want to do whatever I can to speak out about Alzheimer's disease. I have traveled to Washington to meet with my Senators and Representatives and I am testifying here today to urge you to continue the investment in research so that we can spare my children and grandchildren and the children and grandchildren of other Alzheimer families from this devastating disease. We are in a race against time and we need your help!

Thank you.

Senator SPECTER. Mr. Carlino, your comments are obviously overwhelming, and we are very sorry to hear what has happened to you, and we know that your situation is representative as to what has happened to so many, many Americans, and people really around the world, and we hear you, and we are dedicated to doing everything we can through Federal assistance, to funding, to assist you.

If the assistance can come in time for you and for Ms. Reid, who comments about being 15 years away from her mother's age, and of course you are there. When you talk about your losing your practice because you could not think properly, I would be interested and I think others would be, too, to know just what happened to you when you, as you put it, could not think properly.

Mr. CARLINO. Senator, when you have a business, it is probably the toughest way for somebody to analyze that you have Alzheimer's or that something is wrong because you have many people performing tasks for you. In other words, in the morning my secretary would run down my list of appointments. When I would misplace things or I would forget things, it did not register because there was somebody else to pick up for me.

But sending out proposals, Senator, I was at a point where—when I graduated high school I had an IQ in excess of 150, OK? I could do algebra, geometry in my head. When I was in the service

I was a member of the special operations unit in S–2 and had to commit a lot of information to memory. When it got to a point where I was sending out proposals, I used to be able to bring in one job for every three proposals or presentations that I went on. I was sending out proposals and was not getting short-listed on one out of 50.

And if you take a look at them now, you can understand because when I put the proposals together I was forgetting to put in all the proper information.

Senator SPECTER. Mr. Carlino, what are your doctors doing for you at the present time?

Mr. CARLINO. I am on Aricept, I am on Prozac, I am on BuSpar, all to help my mood. I undergo neurological testing once every 3 months, and I see my primary physician once every 3 weeks.

Senator SPECTER. Dr. DeKosky, a two-part question. What can be done for Mr. Carlino now and what can be done for Mr. Carlino with increasing the funding to $100 million more than the $466 million?

Dr. DEKOSKY. For Mr. Carlino now, the only medication specifically approved for the treatment of Alzheimer's disease is Aricept. He is on that medication. There is one more medication for symptomatic treatment that will come onto the general market in either May or June. There probably is a third currently before the FDA which will, if it is approved, be generally available in the year 2001.

Senator SPECTER. A third product?

Dr. DEKOSKY. A third symptomatic treatment medication. The vitamin E trial that was one of the first trials that showed we could at least affect the course of the disease, which was completed 2 years ago, is another medication to try. But for people like Mr. Carlino who are as articulate as he is now and who show the face of Alzheimer's disease that people do not think about, people who are still quite normal and quite able to interact every day, the slow—the progression medication trials, the mild cognitive impairment trials are exactly targeted toward. They are the people who we are trying to have the disease stop in.

We think that the same medications that work for slowing down, frankly, symptomatic Alzheimer's disease should work in mild cognitive impairment. We would probably have to test them separately, but there is no question that we would try them immediately and rapidly. But when I tell you about the imperative of time, and the fact that, for example, to conclude a mild cognitive impairment that starts today would probably take us a minimum of 3 years, we have a problem helping Mr. Carlino as quickly and as effectively as we would like to do.

Now that science has been the success that it has, to say here are the medications that are safe enough and presumably effective enough to be put into trials, the medication to run those long and expensive trials would have to simply come out of the monies which have already been budgeted for the science and the other clinical trials.

The major focus of this request for an increase is to build on the successes that we have had and start the clinical trials now, because ones that start today for mild impairment probably cannot

be completed in less than 3 years, and the primary prevention trials would probably take a minimum of 5 years, and they cost $15 to $20 million each. If we string them out 5 years at a time, we will be in the middle of that epidemic before we have answers.

Senator SPECTER. Dr. DeKosky, sometimes the medicines are pretty well established even before FDA gives final approval. You say there are two in that category. Is it worth exploring? Let me ask you to do this. My red light is on. I have one more question before yielding to Senator Harkin. Would you talk to Mr. Carlino and see if either of those two—sometimes it is possible to shake loose some of that from the FDA.

Dr. DEKOSKY. I will do that, certainly.

Senator SPECTER. I know he has his own doctors, but I doubt that he has doctors with your pedigree. So if you would talk to him, I would appreciate it.

Dr. DEKOSKY. I will do so.

Senator SPECTER. The one other question I have before yielding to Senator Harkin is a similar question for Ms. Reid. She has given us a chronology of 15 years. What can be done for Ms. Reid?

Dr. DEKOSKY. Well, Ms. Reid is—actually along with other baby boomers, and one of the best guarantees we have the research will be done is that many of the leading scientists now are boomers who are looking at that age of risk—is, these studies are directed toward these people. These studies, the primary prevention and the mild cognitive impairment trials are directed toward the group who is currently now between 50 and 65. It is to know whether or not we can stop the progression in people over 65 that would let us know that either in their 50's or when they reach a significant age of risk, which is 65 to 70, you could put people on safe and effective medications that would effectively delay the onset of the disease until after their normal life expectancy.

So although we talk about and we would be happy to have a 5-year delay, that would save about $50 billion a year, about 50 percent of the current burden, if we had a 10-year delay, which based on some of what we know about reversibility in brain or slowing progression down in brain is achievable, we probably could eliminate up to 80 percent of the disorder. We will not catch everybody. There is no disease for which we have effective treatments where we could realistically expect to stop everybody, but we certainly could launch the equivalent—for example, if it were vaccine or medications, that we do for pneumonia vaccinations or flu vaccinations and other sorts of highly successful and economically advantageous public health measures.

Senator SPECTER. Senator Harkin.

Senator HARKIN. Thank you, Mr. Chairman. The question I had for—well, first of all, I know there are a number of Iowans who are here, and it is estimated over 68,000 Iowans are now suffering with Alzheimer's disease. You know, it affects us all. I just listened to your stories.

My grade school teacher, Mary King—well, she was Mary Powers then, Mary King later—lived right across the street from me in a small town in Iowa, and until a year ago, a year ago she was just fine. And lived by herself, but right across the street lived my

brother, who is disabled, and she was always kind of looking after my brother.

I just visited Mary King last month—I am sorry, in January. And she has to be in an Alzheimer's unit of a nursing home, which is locked up so she does not wander off because she gets lost and does not know how to get back. And just to see how rapidly it happened, in 1 year. A year ago she was just—you could not tell. So while I have thought about Alzheimer's as being a slow progression, I am wondering what happened there? How come sometimes it is so rapid like that, Dr. DeKosky? Is this just another form of Alzheimer's?

Dr. DEKOSKY. Senator, my first question is how old is Ms. Powers?

Senator HARKIN. Well, Mary must be about 78 or 79 right now.

Dr. DEKOSKY. Mr. Carlino's comments about the fact that there were people around to help him or that things happened so slowly that he did not notice it applies in many cases to people especially who are elderly who maintain themselves well. Two things happen.

If you have lots of help, people think you are idiosyncratic or eccentric if you are very wealthy, and they take care of the things you forget. And if you do not have much help you actually usually fall earlier or if no one is watching you. So it may well be that she had symptoms and that as a highly intelligent and educated teacher, she had sufficient brain reserve, such as I think Mr. Carlino clearly demonstrates, and that when she exhausted that reserve, she became symptomatic relatively rapidly.

I do want to make one more comment, although you were not here, Senator, for that testimony, it had to do with Senator Specter's question about the testing for ApoE4. The reason I asked you about her age was that although ApoE4, not unlike stem cell research, is teaching us tremendously useful things about the processes that happen in the brain in neurological disease, most of the risk of ApoE4 occurs in people who have onset before age 80. And that if we look at people over 80, especially this big group over 85, there is very little ApoE4 effect in that group, and they are actually a major group that we are targeting.

So although in the clinics the people who come in are younger and it makes it look as if the ApoE4 has a very strong effect in the whole population, in fact, it is applicable as a risk to our younger people below 70, and I would say below 75, but it is not a risk for this other large population who are over the age of 80. And that is one of the other reasons why it is a mixed blessing.

People think that it will tell them the definitive yes-no if we test them. And so we either can engender a false sense of security since more than 50 percent of the people who get it do not have ApoE4 or we can make people worry. And we do not yet, Senator, have the effective treatments that if we screened the population for E4 positive people, we would say we are going to put you on this medication at this point in time. And I think that is why all the groups who have issued advisories have cautioned against examining asymptomatic people.

Senator HARKIN. Dr. DeKosky, I understand you have received a grant from the National Center for Complementary and Alternative Medicine to study the effect of ginkgo biloba on dementia. How far

along are you in studying the effect of this supplement and could you also talk about vitamin B and what kind of promises are these type of therapies showing for the prevention or at least the alleviation of Alzheimer's disease?

Dr. DEKOSKY. Thank you, Senator. The ginkgo biloba trial I believe will get underway with recruiting patients as subjects because these are normal people, probably in May or June, in four cities around the United States; in Pittsburgh, in Winston-Salem, South Carolina through Wake Forest, and Hagerstown through Johns Hopkins, and in Sacramento through the University of California-Davis. They are the centers of the cardiovascular health study, which is an add-on, saving us money. It is a structure that had been around for 10 years that we are now going to do this study over the top of.

There are reasons that we think ginkgo biloba might be helpful in Alzheimer's disease beyond its 1,600-year history. It has antioxidant properties. It also thins the blood very slightly. But we have not proven that it works and we cannot until we try it. But it will take us 5½ years to complete that study because we are doing it in normal people over the age of 75, and on average only 1 percent to 2 percent, perhaps 3 percent of normal people convert to Alzheimer's every year.

So we not only need 3,000 people that we have to see every 6 months, we have to see them for 5½ years before enough people convert to Alzheimer's who have either real drug on board or placebo and then test the statistical difference between the two groups. That is why we cannot do these studies strung end to end.

Senator HARKIN. My red light is on. Can I have one more, quick? I have a good softball here for you, Dr. DeKosky. The Senate and House are currently conferencing, and I am one of the conferees, on the Patient's Bill of Rights legislation as it is called. Both bills currently contain provisions to allow patients to access clinical trials by requiring insurance companies to pay the routine patient care costs associated with these trials. However, the Senate bill limits access to the trials to cancer patients only, while the House bill allows participation for patients with all diseases, including Alzheimer's.

Dr. DeKosky, as a researcher, can you tell me if there is any scientific rationale for limiting reimbursement for the routine costs of clinical trials to cancer patients only?

Dr. DEKOSKY. No, sir, I cannot.

Senator HARKIN. I told you it was a softball.

Dr. DEKOSKY. I am sufficiently stunned by the logic of that that it took me a moment to answer. But, no, there is no reason. In fact, it would probably be a real synergy with the research community for all medical diseases.

Senator HARKIN. I wanted to make that point. With so many people here and with this bill now being conferenced, that—I wanted to make that point, that why limit it only to cancer patients? It should be open to all, and for clinical trials.

The project you have ongoing with ginkgo biloba and things like that, you said it would take a long time. These kind of trials should be open to all people and not just limited. I just hope people understand that, and, what the heck, I mean, you are in the right place

to see your Congressmen and Senators about that, so I urge you to make your interests in this known on that one specific thing. I will make it very clear to all of you again in the audience, that—as this Patient's Bill of Rights gets hammered out in conference, that to make it make clinical trials accessible to all and covered by the insurance companies and not just to cancer patients. So if you will do that for me, I would sure appreciate it. Thank you. I am sorry, Ms. Reagan?

Ms. REAGAN. Senator, you mentioned something about your friend in Iowa that, I thought it would be a nice time for us to mention something we do in the Alzheimer's Association. We have a safe return program which takes about a million dollars in the Department of Justice budget every year, but it is an identification bracelet that is registered with local police, just like Mr. Carlino has here, and this way if somebody does wander or gets lost, we can get them home. And we are very proud of that program, and we want to be sure everybody gets home safely.

Senator HARKIN. I have heard of that. Thank you. That is a good point. That is in the Justice Department? That is funded out of the Justice Department?

Ms. REAGAN. Yes.

Senator HARKIN. About a million a year, you think?

Ms. REAGAN. About a million, yes.

Senator HARKIN. We will have to keep our eyes on that one, too.

Senator SPECTER. We shall. That comes through another subcommittee, but we will take a look at it.

Senator HARKIN. Yes, not ours.

Senator SPECTER. We thank you all very much for coming. Dr. DeKosky, if you would supplement your testimony with a written response to the questions I asked Dr. Hodes, what do you think, how many of those 78 percent ought to be funded, what the cost would be, what you think a budget would be to do the job totally.

Dr. DEKOSKY. Yes.

Senator SPECTER. Appreciate that. And Ms. Reagan, we thank you very much.

Ms. REAGAN. Thank you, Senator.

Senator SPECTER. I know that my colleagues all would ask that you send our best to your father when you see him again.

Ms. REAGAN. I certainly will.

Senator SPECTER. Ms. Reid, we thank you for coming. Mr. Carlino, we got you another doctor today.

Mr. CARLINO. Thank you.

Senator SPECTER. And to the extent that we can focus in on your condition as you are, we want to preserve you much beyond 58, and we want to preserve that 150 IQ, a great rarity.

Mr. CARLINO. Thank you.

CONCLUSION OF HEARING

Senator SPECTER. Thank you all very much for being here, that concludes our hearing. The subcommittee will stand in recess subject to the call of the Chair.

[Whereupon, at 10:25 a.m., Tuesday, March 21, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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